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Synergistic catalysis in asymmetric synthesis of polysubstituted pyrrolidines

Tesi di laurea sperimentale

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ABSTRACT

This thesis deals with the feasibility of synthesizing stereodefined polysubstituted pyrrolidines in a formal [3+2] cycloaddition, starting with vinylciclopropanes (also called VCP) with two geminal electron-withdrawing groups (EWG), employed to make formal 1,3-dipole, and imines, used as dipolarophiles.

This synthesis is based on the so called synergistic catalysis, that could be described as the combination of two catalytic species, each one able to activate one reaction partner. The former catalyst is a palladium complex, capable of activating the VCP by forming the aforementioned 1,3-dipole via oxidative addition. The latter, instead, is a chiral Brønsted acid, like a BINOL-derived phosphoric acid or triflamide, which not only makes the imine more electrophilic, but can also induce the preferential formation of a diastereoisomer over the other one and even enantiomeric excess within the diastereomeric couples, thanks to its axial chirality.

1 INTRODUCTION

1.1 Asymmetric synthesis

Asymmetric or enantioselective synthesis is a chemical reaction in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric products in unequal amounts[1]. The principle on which enantioselective synthesis is based, is that, even if the products (i.e. enantiomers) enthalpic and entropic values are the same, another chiral molecule can interact with one or both of their transition states, modifying the energetic pathways and thus, it leads to preferential formation of a product on the other (*Figure 1*). The interest in this field is due to the relevance that optical purity has, for example, in drug efficiency and safety, since two enantiomers, which have the same chemical and physical properties, could interact very differently with substrates in biological environment.

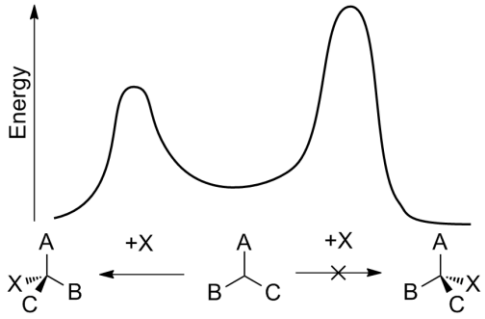


Figure 1: Generic pathways of two enantiomers formation, which transition state energy has been altered by a chiral catalyst (X).

1.2 Organocatalysis

Many kinds of catalysts have been employed to obtain the selectivity described in the previous section, as organometallic complexes or biological enzymatic systems. These have positive features, such as low catalytic loading and high turnover number or frequency, counterbalanced by some drawbacks, such as the high cost, recovery and disposal issues and sensitivity to environmental conditions (e.g. water and oxygen). For these reasons, a branch of catalysis, just called organocatalysis, has taken place, thanks to the low cost and wide availability of the catalysts, that are small molecular weight organic molecules, which come directly from natural sources, or they are made by simple synthetic steps. Starting from Cinchona alkaloids, L-Proline and their derivatives (see two examples in *Figure 2*), already used since "60s[2,3], an exponential growth in number and kind of these catalysts has taken place for the aforementioned reasons. Organocatalysts can be divided

into some classes: the ones derived by natural compounds and those obtained synthetically. Furthermore, there are those whose mechanism is based on covalent bond formation and those based on weak interactions or Brønsted acidity, which behaviour is better explained in section 1.5.

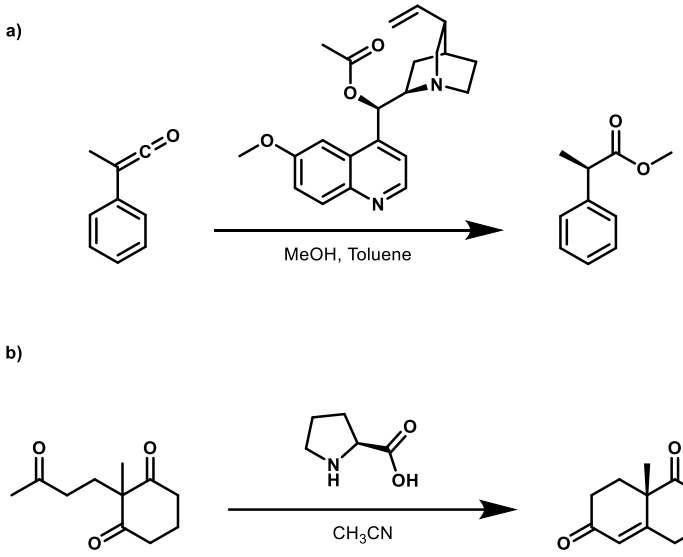


Figure 2: ***a)*** *Acetyl-quinine catalysed addition of MeOH to a ketene.* ***b)*** *L-Proline catalysed Robinson annulation. Two of the milestones of organocatalysis, where the obtained products are enantioenriched.*

1.3 Synergistic catalysis

In standard catalytic reaction, the role of the catalyst, usually just a single molecule, is to reduce activation energy of a specific reaction, creating a different path that means, for example, lowering the LUMO of an electrophile or raising the HOMO of a nucleophile separately. In this project the synergistic catalysis (belonging to the so called multi-catalysis ensemble) is studied[4], where there are two active species working together to reduce the energy gap between frontier orbitals of two substrates by interacting with both of them simultaneously, as each catalyst is designed to interact with one reaction partner[4]. This type of catalysis owes its name to a synergic effect occurring in the aforementioned combined mechanism, in which, lowering energy gap, decreases activation energy (*Figure 3*), positively affecting rate constant in kinetic equation, and it drives the desired pathway in preference to possible side reactions[4].

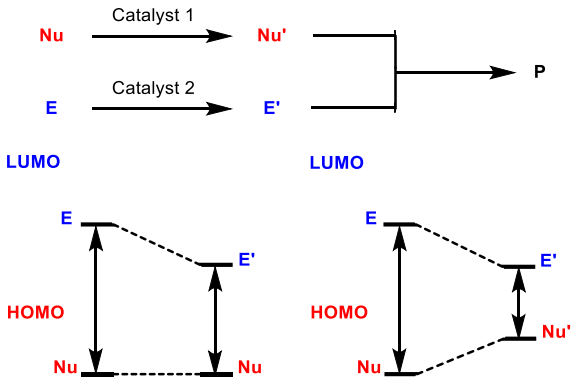


Figure 3: A schematic concept of synergistic catalysis.

In this project, one of the catalyst of the couple is a palladium complex, capable of activating a vinylcyclopropane by forming a formal 1,3-dipole via oxidative addition (see section 1.4 for further details). The latter is a chiral Brønsted acid, like a BINOL-derived phosphoric acid or triflamide that, not only lowers electrophilic substrates LUMO, but can also influence stereoselectivity in the products, thanks to its axial chirality, as explained in section 1.5.

1.4 Vinylcyclopropanes reactivity

Vinylcyclopropanes (also called VCP) are known since 1959 and studied in rearrangement reactions, usually leading to cyclopentene formation (*Figure 4*)[5].

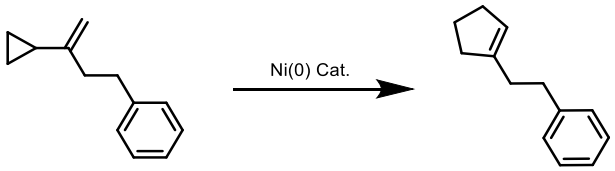


Figure 4: An example of VCP rearrangement leading to cyclopentene formation.

In fact, only in the last decades, the interest towards them increased and many other possibilities have been explored, as annulation or substitution, intramolecular or intermolecular formal cycloaddition with several electrophilic substrates. In this context, VCP reactivity is highly increased if there are two germinal electron-withdrawing functional groups on the 2-position of the ring. Two EWG-substituted VCP are much better than mono-substituted ones, both for electronic reason and for Thorpe-Ingold effect[6], that allows the compounds to be more stable and, at the same time, more prone to unveil their nucleophilic position. In order to further increase the aforementioned reactivity, VCP are often employed in metal-catalysed reaction, due to 1,3-dipole formation (*Figure 5*), that greatly enhance their nucleophilic behaviour[9].

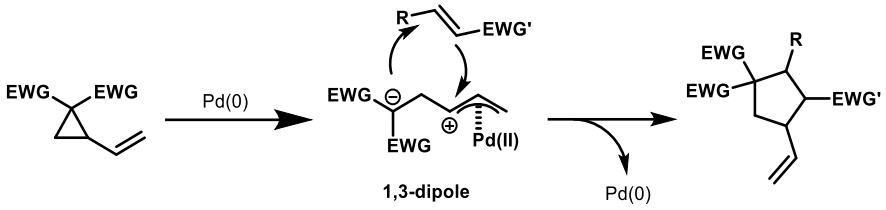


Figure 5: 1,3-dipole formation through the insertion of Pd catalyst within the vinylcyclopropane ring and reaction with a generic electrophilic partner, forming a 5-members cycle with the restoration of the free catalyst.

Among all the low valent metal catalysts, as Fe(0)[7], Ir(0) and Ni(0)[12], Pd(0) complexes aroused more interest for their higher activity and versatility in important reactions like formal [3+2] cycloadditions[8], as the one shown in *Figure 6*[5,9], where an organocatalyst is involved in a synergistic catalysis mechanism (generally described in the previous section). Therefore, combined to a palladium complex, it further lowers the gap between substrates frontier orbitals, speeding up the reaction and driving it to higher yield. Moreover, thanks to catalyst chirality, product stereoselectivity is also favoured, nearly reaching enantiopurity.

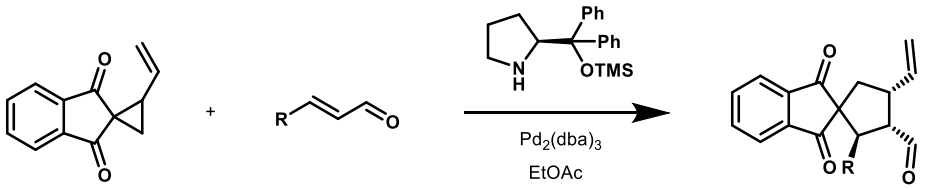


Figure 6: Formal [3+2] cycloaddition of α,β-unsaturated aldehyde to VCP, an example of synergistic catalysis in which both an organocatalyst and a metal complex are used.

1.5 Chiral phosphoric acids catalysis

Lewis acids are widespread catalysts, due to the enhancement of electrophilic behaviour in carbonylic or similar compounds, obtained by the coordination to heteroatom non-bonding orbitals. Many studies reported good enantioselection achieved by using a chiral Lewis acid as catalyst[10]. In the last few years, besides the aforementioned compounds, chiral Brønsted acids have become more and more studied as organocatalysts, as they are able to activate electrophilic substrates as much as Lewis counterpart. The mechanisms by which these acids act, could be different, according to the acidity level of the catalyst itself. Weak Brønsted acids, like TADDOL, ureas or thioureas, work in a general acid catalysis (GAC) fashion (*Figure 7a*), activating the target molecule by hydrogen bonding. Instead, stronger acids, as BINOL, phosphoric acids or triflamides, work in a specific acid catalysis (SAC), transferring their proton to the substrate, which become more electrophilic, gaining

a positive charge (*Figure 7b*). Obviously, the real mechanism is always an intermediate shade of these two limit cases.

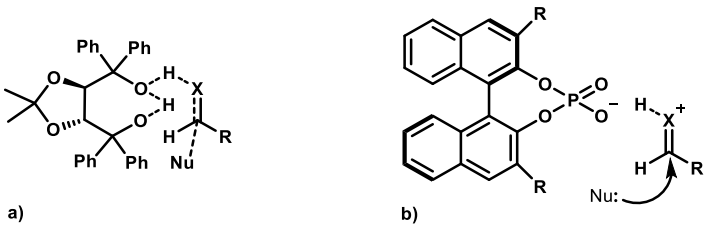


Figure 7: ***a)*** *An example of GAC explained by using TADDOL.* ***b)*** *An example of SAC using a chiral phosphoric acid.*

Essential in this project are the synthetically obtained chiral phosphoric acids, characterized by a high Brønsted acidity ($pK_a \approx 1$), conjugated to Lewis basicity of the phosphate group. Moreover, they are characterized by axial chirality, due to the hindered rotation of the bond between the two biarylic moieties, keeping them to a fixed angle[11]. This feature plays a crucial role in achieving high stereoselectivity, where modifying 3,3'-positions substituents alters hindrance and electronics. In this work, where imines are chosen as electrophilic partner in Mannich-type reaction, chiral phosphoric acids and triflamides with different substituents are tested to reach stereoselection in the product.

2 AIM OF THE PROJECT

The aim of the project is to study and develop a new catalytic enantioselective reaction between vinylcyclopropanes (VCP) and imines, exploiting the synergistic combination of palladium catalysts (for VCP activation) and phosphoric acids or triflamides (able to activate imines), according to the mechanisms described in the previous chapter and displayed by *Figure 8*. Some organometallic catalysts based on iron and nickel have been reported to promote the cycloaddition between VCP and imines.[7,12] However, the application of chiral organometallic species (that is nickel biphospshine complexes) has only resulted in low to moderate enantioselectivities. In this project, motivated by the great importance of these products in different chemistry fields, it was envisaged that synergistic catalysis (never applied to this specific reaction) could provide a unique opportunity to develop a highly enantioselective version of this reaction. In order to reach this goal, a lot of parameters and conditions have to be changed, as temperature, solvents, substrates, catalysts structure and electronic properties (e.g. 3,3'-substituents on chiral phosphoric acid, Pd source and ligands), ratio and loading.

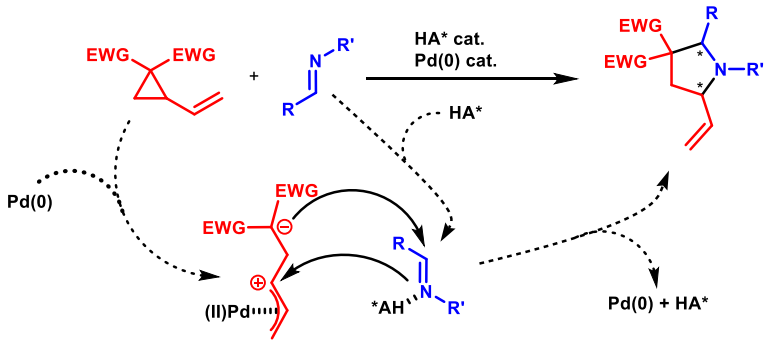


Figure 8: Synergistic mechanism of a Pd(0) and a chiral phosphoric acid/triflamide catalysing polysubstituted pyrrolidine synthesis from a VCP and an imine.

3 RESULTS AND DISCUSSION

3.1 Substrate screening

This project of thesis began with the research of suitable partners for vinylcyclopropanes, able to react with them, giving products that can be purified and analysed, in order to find a convenient reaction platform for the subsequent optimization. To this purpose, VCP **2b** (see section 5.2 for synthesis procedure), has been used, in the presence of a palladium catalyst, in order to test its reactivity with some electrophilic (dipolarophilic) substrates, such as electron-deficient olefins, imines and isoquinoline. Electron-deficient olefins showed good reactivity with the aforementioned VCP **2b** (*Figure 9*); however the products were always formed as complex diastereomeric mixtures (three diastereoisomers in nearly equimolar amounts), thus making NMR and HPLC analysis a difficult task.

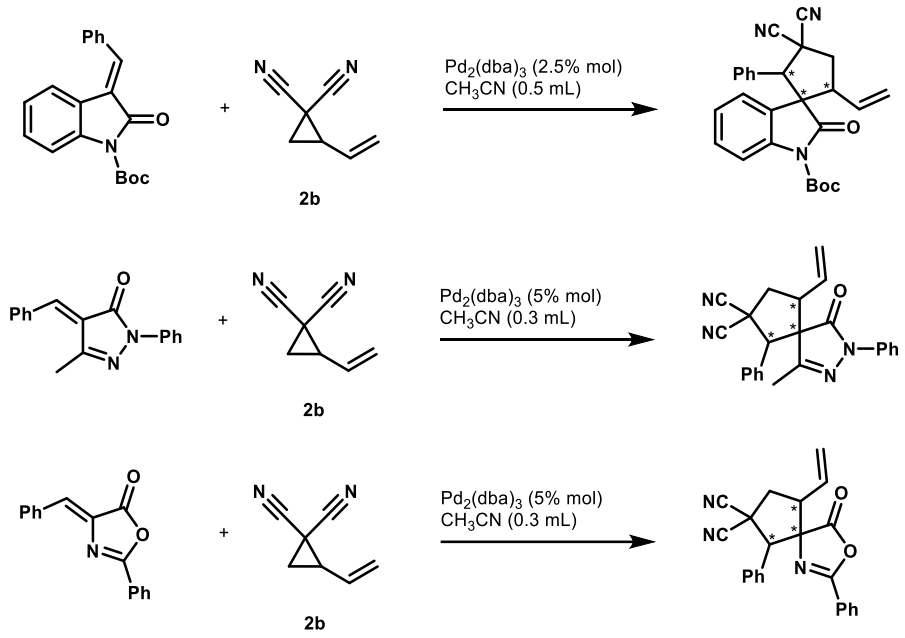
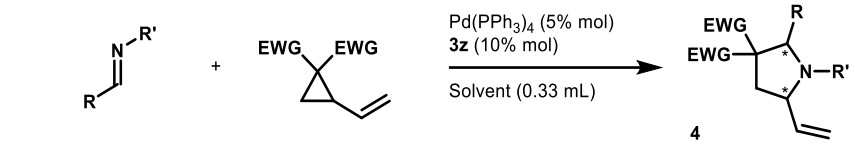


Figure 9: Some examples of reaction with substrates that were discarded.

Also imines were found to be proper partners for VCP **2b**, as they achieved complete conversion in a relatively short time and, above all, the polysubstituted pyrrolidines obtained as products display only two chiral carbons and, consequently, two couple of diastereoisomers, unlike the products shown in *Figure 9*. This has considerably simplified their analysis and, thus, led us to select these compounds for the development of synergistic catalysis in vinylcyclopropane chemistry.

In particular, imines **1a-d** have been tested with the dipole precursors **2a** and **2b**, in order to understand which is the most promising system to allow the development of an enantioselective reaction.

Table 1



1a: R' = -PMP; R = -Ph
1b: R' = -Ts; R = -C_2H_2-Ph
1c: R' = -Ts; R = -Ph
1d: R' = -t-Boc; R = -3-Py

2a: EWG = -CO_2Me
2b: EWG = -CN

Entry	1	2	Solvent	Conversion[a]
AG007	**1a**	**2a**	CH_3CN	>99
AG008	**1b**	**2a**	CH_3CN	0
AG009	**1c**	**2b**	CH_3CN	>99
AG010	**1d**	**2a**	CH_3CN	0
AG011	**1c**	**2a**	CH_3CN	>99
AG012	**1a**	**2a**	CH_3CN	>99
AG013	**1c**	**2b**	Toluene[b]	>99
AG014	**1c**	**2a**	Toluene[b]	>99

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *The solvent is previously dried by pellets of 3Å molecular sieves.*

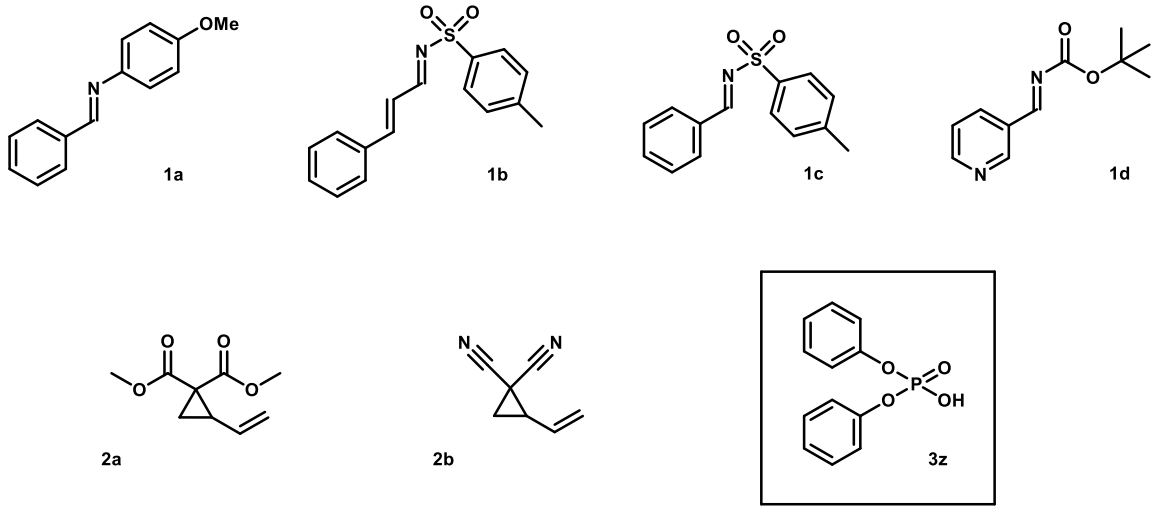
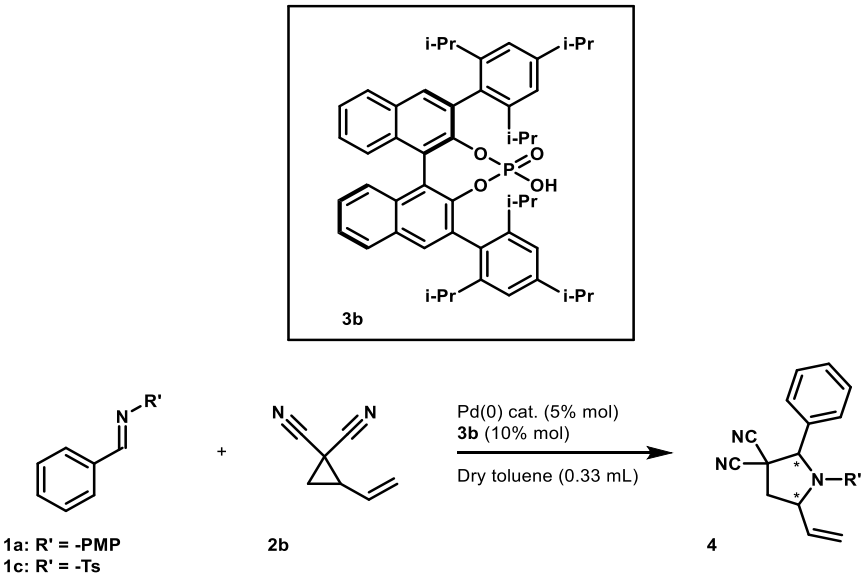


*Figure 10: Some of the tested imines (**1**), VCP (**2**) and the racemic phosphoric acid (**3z**).*

From the values reported in Table 1, **1b** and **1d** could be discarded, as they did not afford the products, while **1a** and **1c** went to complete conversion both in reactions with **2a** and with **2b**, in acetonitrile and in dry toluene, indicating they could be some good partners of VCP. Then, using the aforementioned substrates, a common reaction scheme (section 5.5) was built, in order to test the stereoselectivity of these reactions in the presence of a representative chiral phosphoric acid (CPA) **3b**. From now on, stereoselectivity values are reported by diastereomeric ratio (**d.r.**) and enantiomeric excess (**ee**).

Table 2



Entry	1	Pd(0) cat.	Conversion (%)[a]	d.r.[a]	ee 4-maj (%)[b]	ee 4-min (%)[b]
AG015[c]	**1c**	$Pd(PPh_3)_4$	>99	1:1.5	Rac	Rac
AG016	**1c**	$Pd_2(dba)_3$	0	\	\	\
AG017	**1c**	$Pd(PPh_3)_4$	>99	1:1.4	Rac	8
AG018	**1a**	$Pd(PPh_3)_4$	>99	1:0.1	10	48

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *CPA is not used in this reaction, in order to test the reactivity of the dipolarophilic substrate.*

The nitrogen atom of compound **1c** is substituted by an electron-withdrawing group such as toluenesulfonyl, which is able of enhancing carbon electrophilic behaviour and, theoretically, should promote Mannich-type reaction. Nevertheless, as **1c** is a very strong electrophile, it does not need to be activated by a phosphoric acid (as shown in ***AG015***), in

the way described in section 1.5 and, for this reason, it leads to racemic mixture of products. Therefore, imine **1a** has been chosen for further tests, as PMP group has electron-donating effect that makes this substrate less reactive and, for this reason, more prone to be activated by the chiral catalyst, which could direct the stereoselectivity of the reaction. While the aforementioned imine is meant to be the proper electrophilic substrate, others VCP are synthesized (detailed procedure is described in section 5.2) in order to test them with it.

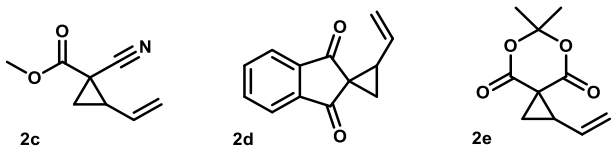


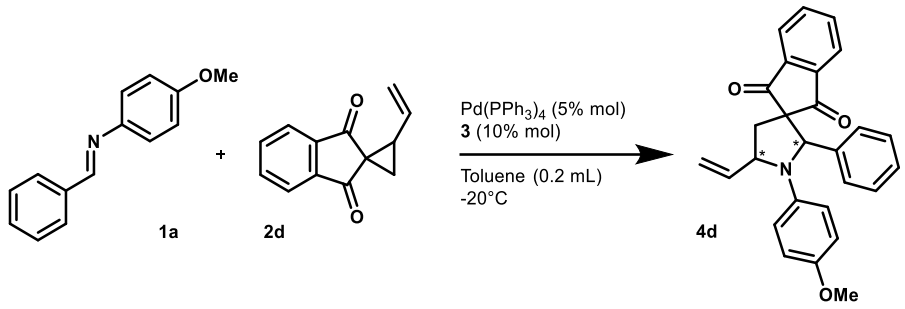
Figure 11: Other VCP synthesized in order to test them with the imines.

As **2c** leads to a product with three chiral carbon and, hence, three diastereoisomers, it was rejected as the substrates shown in *Figure 9*, since it furnished extremely complex NMR spectra. Then, **2e** was also discarded, as it shows good reactivity, but, together with the imine, forms products that badly separate through several HPLC columns in different conditions.

Finally, **2d** was chosen as a good nucleophilic partner in this kind of reactions, as demonstrated by Rios' work[5], perhaps due to the presence of a planar cyclic diketone as EWG on the 2-position of vinylcyclopropane, that greatly enhances α-carbon nucleophilic behaviour and further defining its angle[6]. Besides the aforementioned qualities, the obtained diastereomeric couples of the product show also well recognizable signals at NMR and HPLC analysis.

Once the aforementioned VCP and imine have been chosen as good substrates of the reaction, some chiral phosphoric acids (CPA) have been tested to understand which one could lead to highest stereoselectivity (Table 3).

Table 3



Entry	3	Conversion (%)[a]	d.r.[a]	ee 4d-maj (%)[b]	ee 4d-min (%)[b]
AG022	**3g**	>99	1:0.4	22	Rac
VC0232	**3b**	>99	1:1	Rac	37
VC0257	**3f**	>99	1:1	24	47
AG025	**3e**	>99	1:0.6	Rac	Rac
AG026	**3j**	>99	1:0.9	Rac	Rac
AG033	**3a**	>99	1:1.3	47[c]	Rac

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *This value is overestimate, due to the superposition of the peaks in HPLC analysis.*

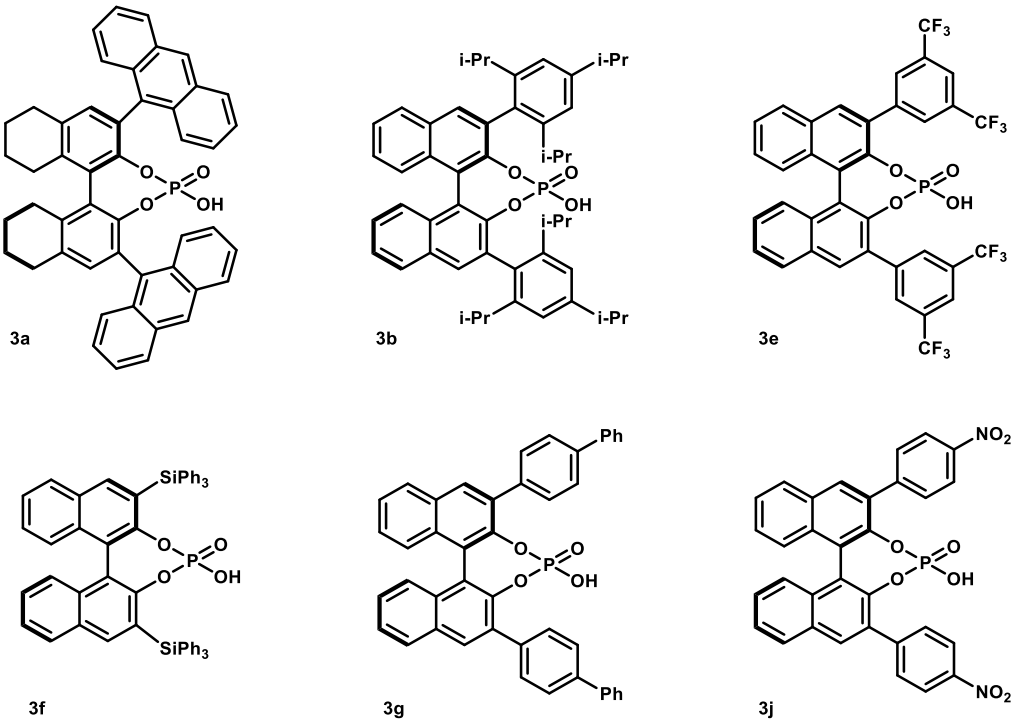


Figure 12: Some of the chiral phosphoric acids used in this work. The complete structures list is reported in Figure 14.

Nevertheless, despite every reaction went to complete conversion, an undesired phenomenon has occurred: pyrrolidines lack of configurational stability, as you can see in Table 3, where diastereoselectivity is always very low, and acceptable values of enantiomeric enrichment are only referred to the minor diastereoisomer. It is possible to hypothesise that the low values of stereoselectivity are due to product epimerization, as shown in *Figure 13*, as the mechanism is enhanced by the strong electron-donating effect of the PMP group.

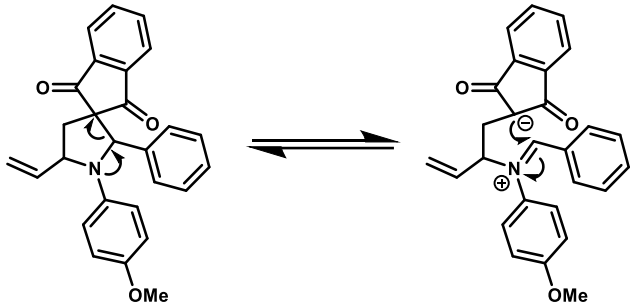


*Figure 13: Epimerization mechanism of **4d,** obtained by reaction between **1a** and **2d**.*

Hence, considering the poor results obtained until this moment by both EWG and EDG substituted imines, diphenyl-methanimine, named **1e** (obtained by procedure described in section 5.3), has been tested. Phenyl group seems to be a better N-substituent than PMP, for a weaker donating effect, and much better than toluenesulfonyl, as it makes the substrate much less electrophilic and, then, an acid catalyst, such as the aforementioned CPA, is required for its activation[11]. Moreover, the so obtained pyrrolidines are promising for the aim of setting up an enantioselective reaction, as they are stable and remain stereodefined, even when they are characterized after months of storage. Nevertheless, epimerization occurs when they are left in acid environment, such as $CDCl_3$, used for NMR analysis, where one diasteromeric couple converts in the other.

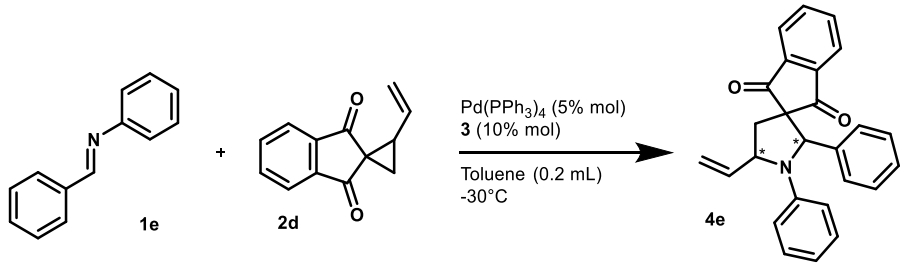
As the proper reaction substrates have been chosen, parameters and conditions could be changed in order to optimize reaction yield and stereoselectivity, developing a good synergistic catalysis pathway.

In the first place, every reaction catalyzed by chiral compound has been ran at -30°C, in order to slow it down, lowering kinetic constants, hence, inhibiting epimerization or decomposition. However, they are still fast, reaching complete conversion in less than two hours. Lower temperatures were not employed, being afraid of possible precipitation phenomena, besides reaction rate decrease, although that could have led in principle to higher stereoselection parameters.

3.2 Catalysts screening

Once reaction substrates have been found, some chiral phosphoric acids were tested, in order to develop an enantioselective version of this reaction. The differences among them, that could possibly enhance reaction stereoselectivity, are related to 3,3'-position substituents of the diaryl moiety, as described in section 1.5, which hindrance and electronic behaviour influences the binding of the catalyst to the imine, involving different transition states and modifying stereoselectivity results[11]. Hence, the reaction was performed according to the procedure described in section 5.5, and the results are compared by NMR spectra and HPLC chromatograms.

Table 4



Entry	3	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG040	**3a**	>99	81	1:3.2	42	11
AG041	**3b**	>99[c]	95	1:1.8	Rac	-17
AG042	**3c**	>99	93	1:0.8	Rac	Rac
AG046	**3d**	>99	82	1:2.0	-13	Rac
AG047	**3e**	>99	81	1:0.4	-10	Rac
AG048	**3f**	>99	87	1:1.8	-10	Rac
AG049	**3g**	>99	88	1:1.5	6	-10
AG051	**3h**	>99	92	1:1.2	-9	-14
AG052	**3i**	>99	86	1:0.5	7	Rac
AG053	**3j**	>99	86	1:0.5	-14	5
AG054	**3k**	>99[c]	87	1:0.6	Rac	Rac
AG064	**3l**	>99[c]	93	1:0.6	Rac	Rac

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *Obtained after natural heating to room temperature and additional 24h of reaction in that condition.*

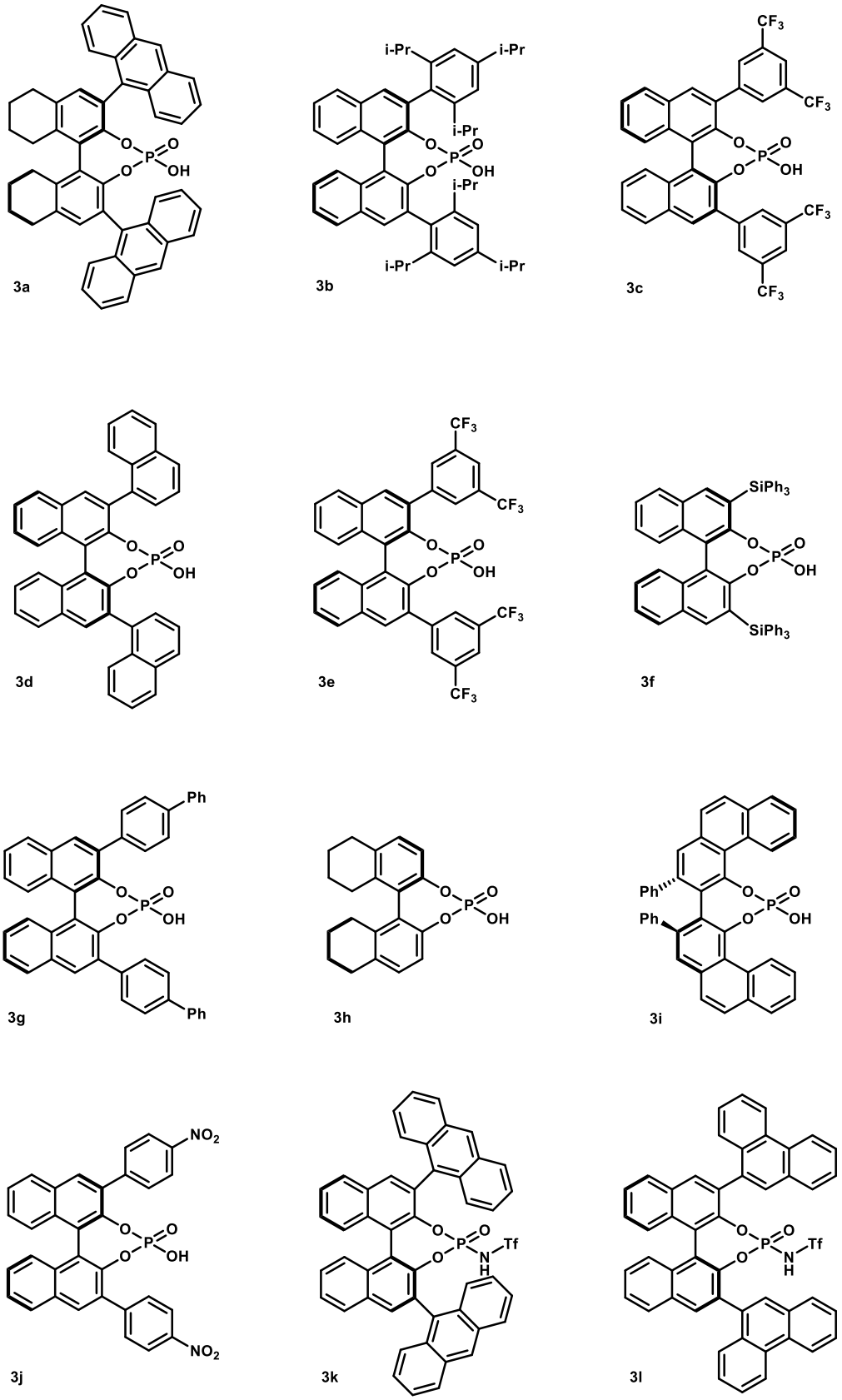
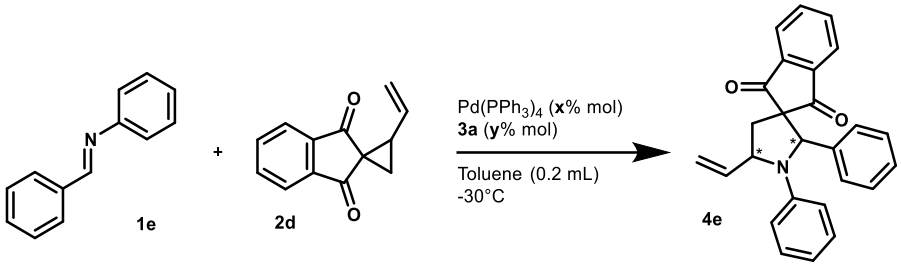


Figure 14: Complete list of all the chiral phosphoric acids and triflamides employed during this work.

As seen in Table 4, the highest values of diastereo- and enantioselectivity were reached by using chiral phosphoric acid **3a**. This could be due to the flatness of the anthracenyl groups, to the presence of saturated rings in the back of diaryl moiety, widening the angle between them, or, more probably, to the combination of these two features, which play a crucial role in this kind of mechanism[11]. Indeed, it can be seen as, for example, **3h** carried the reaction to very low stereoselectivity, because it lacks of 3,3'-hindered substituents, despite its saturated rings. Besides all the simple BINOL-based scaffolds, a vaulted CPA was also tested (**3i**), with poor results, maybe just because its geometry does not fit well with electrophilic substrate or transition state formation. Another catalyst feature that has seemed to affect negatively yield and selectivity of these reactions was having a too high acidity grade, perhaps because it could has promoted epimerization. In fact, the more acidic triflamides, used in a sealed Schlenk tube under nitrogen atmosphere, have shown their reactivity only at room temperature, implying lower d.r. and the obtaining of racemic mixtures.

As CPA **3a** was chosen as proper partner of $Pd(PPh_3)_4$, that has been shown itself a good palladium(0) source in preliminary tests, for the investigated synergistic catalysis mechanism, it was important to understand if there could be a ratio between the two catalysts able to enhance stereoselectivity. Furthermore, once discovered it, it is very important to know which is the minimum level of catalytic loading. Results are reported in Table 5.

Table 5



Entry	$Pd(PPh_3)_4$ (% mol)	3a (%mol)	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG040	5	10	>99	81	1:3.2	42	11
AG057	5	5	>99	88	1:5.3	58	15
AG058	5	15	>99	64	1:2.0	52	-11
AG060	10	5	>99	66	1:7.0	60	35
AG062	5	2.5	≈90[c,d]	\	\	60	32
AG063	10	2.5	≈90[c]	\	\	56	31
AG065	5	20	>99[e]	57	1:1.8	52	-23

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *Crude NMR is very noisy, so conversion is approximately calculated, while yield and d.r. are almost unintelligible.*

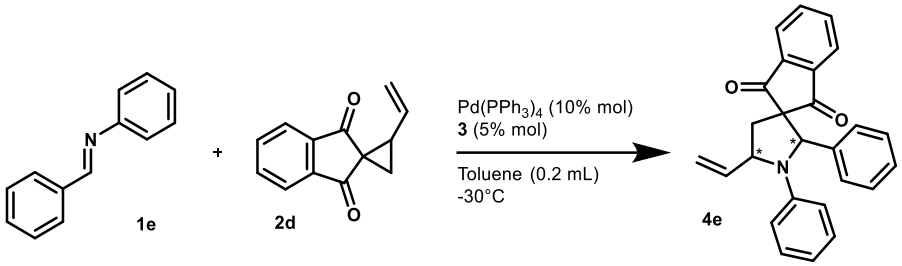
[d] *This value is reached after 2h 30min of reaction.*

[e] *This value is reached after 4h of reaction.*

Starting from reference reaction (***AG040***), deriving from catalysts screening, where Pd/CPA ratio was 1:2, two opposite pathways could have been followed: decreasing or increasing this ratio. A further raising in organocatalyst loading, like in ***AG058*** and even more in ***AG065***, disfavoured d.r. value, only enhancing a little bit of enantioselection. Instead, having reduced phosphoric acid loading, as in ***AG057***, and increased active palladium species, as in ***AG060***, not only has had a more positive effect on the e.e., but also improved diastereoselectivity very much. The limit in decreasing CPA loading was due to the practical difficulty of weighting such a small quantity of the compound (about 0.7 mg at 0.05 mmol scale), besides the fact there has been no further improvement in enantiomeric enrichment, neither maintaining the same ratio, nor taking it to 4:1 – Pd/CPA, as in ***AG063***. The explanation of the aforementioned behaviour could be adduced to the

fact that more active palladium species implies a higher amount of 1,3-dipoles are formed. Moreover, from another point of view, an increase in CPA loading raises significantly the acidity of the system, promoting retro-Mannich reaction in the epimerization mechanism. To understand if any other phosphoric acid catalyst works better than **3a** in the new conditions, **3b**, **3e** and **3f** (*Figure 14*) have been tested with a Pd/CPA ratio of 2:1, as in ***AG060***.

Table 6



Entry	3	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG060	**3a**	>99	66	1:7.0	60	35
AG066	**3b**	≈90[c]	84	1:1.5	Rac	-11
AG067	**3e**	>99	>99	1:0.6	-11	Rac
AG068	**3f**	>99[d]	94	1:3.6	-21	-14

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *This value is reached after 6 hours of reaction.*

[d] *This value is reached after 4 hours of reaction.*

As shown in Table 6, every chiral phosphoric acid tested in the optimized ratio with $Pd(PPh_3)_4$, which has led to stereoselectivity enhancement in the reactions where **3a** has been employed, not only has given worse results in comparison with that, but, except for ***AG068***, even worse than the ones obtained in the preliminary catalysts screening (Table 4). Therefore, this optimization seems to be specific for the catalyst **3a**, which is confirmed as the best catalyst found so far.

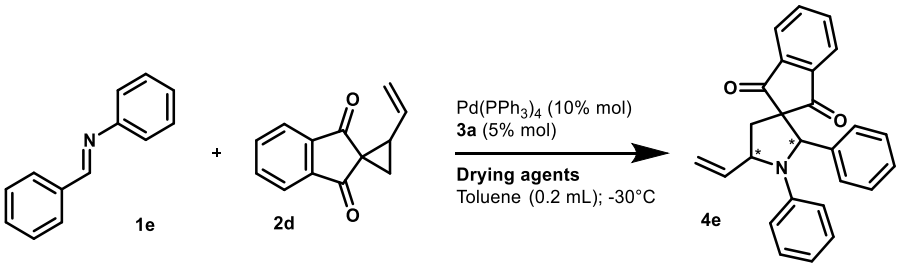
3.3 Optimization of reaction conditions

Once the most stereoselective phosphoric acid and its optimal ratio with $Pd(PPh_3)_4$ were found, some other conditions have been changed in order to understand if they affected the studied synergistic catalysis mechanism and if they could improve it, enhancing stereoselectivity.

The first external parameter that has been introduced is the use of drying agents. In fact, even if they are seldom employed in these type of reactions, where two catalyst species are involved, they have been broadly used in simple phosphoric acid catalysed reactions[11].

The aforementioned drying agents are inserted in a Schlenk tube together with catalysts and reactants under nitrogen athmosphere, in order to see if they bring any benefits to diastereo- and enantioselection (Table 7).

Table 7



Entry	Drying Agent[d]	Conversion (%)[a]	NMR Yield (%)[a]	d.r. [a]	ee 4e-maj (%)[b]	ee 4e-min (%)[b]
AG069	5Å M.S.[c]	>99	56	1:3.2	12	-48
AG070	4Å M.S.[c]	>99	89	1:2.2	10	-53
AG071	3Å M.S.[c]	>99	91	1:2.4	10	-53
AG072	$MgSO_4$	>99	86	1:1.1	49	Rac
AG073	Na_2SO_4	>99	>99	1:4.6	60	51

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *The number indicates the average size of molecular sieves pores.*

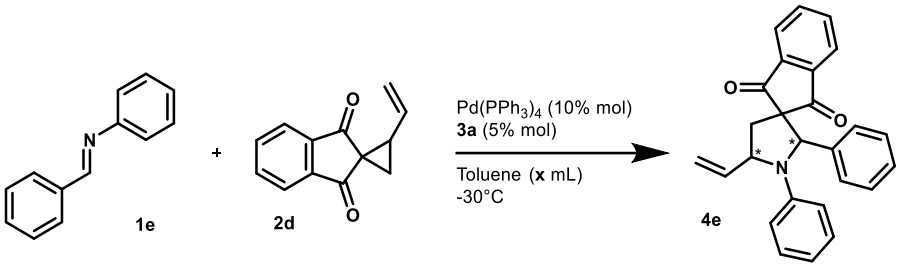
[d] *The quantity of the drying agents is approximately equal to the total amount of reactants and catalysts weight (about 30 mg).*

Using molecular sieves seems ineffective to improve reaction stereoselectivity, as reported in the first three lines of Table 7. The situation got better when sulphates were employed,

in particular when Na_2SO_4 was used, as, unlike magnesium, is not able to coordinate phosphoric acids oxygen. Nevertheless, since there has been no improvement from previous optimized reactions, despite several precautions needed in their set up, the use of drying agents has been discarded.

An important step made during the conditions optimization of the synergistic catalysis mechanism in pyrrolidine synthesis is to see how system dilution or concentration influences stereoselectivity and if it affects any other reactions parameters, such as yield and conversion.

Table 8



Entry	Toluene volume (µL)	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG060	200	>99	66	1:7.0	60	35
AG082	400	>99	80	1:14	62	Rac
AG083	100	>99	>99	1:1.9	61	Rac
AG086	600	>99	79	1:22	65	-11
AG087	800	≈80	66	1:26	60	-14

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

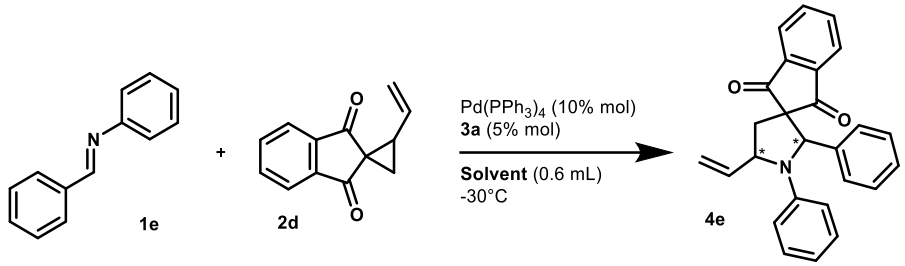
As reaction rate is directly related to reactants concentration by kinetic equation, diluting the system, increases the time needed to reach full conversion from less than an hour, in the most concentrated sample (***AG083***), to almost two hours for the most diluted (***AG087***), which however is, more or less, the time needed in reference ***AG060***. Accordingly to this behaviour, conversion and yield decreased by diluting the system, d.r. become higher and higher, even if it reaches a plateau. Despite this, e.e. value reached its maximum when reactants and catalysts have been dissolved in 0.600 mL of toluene, at 0.050 mmol scale. While the very close enantioselectivity values seem to indicate that concentration does not

have dramatic influence on this reaction outcome, the diastereoselectivity is improved considerably. On the contrary, conversion is slightly reduced, going to higher dilution, maybe just for the aforementioned kinetic reasons.

These tests have represented the most important step in the improvement of diastereoselection, bringing d.r. values to more than 1:20, which means that a diastereomeric couple is highly favoured with respect to the other. While that stereoselectivity parameter has enhanced a lot from reference reaction, enantiomeric excess raised only by five percentage points (65% ee), which is however an improvement, but less important than the expected. Furthermore, it seems that d.r. and e.e. are not as much related as in the previous optimization studies, which means that enantiomeric enrichment is not linearly related to the raise of diastereomeric ratio. Therefore, the moderate e.e. values seems not to be to a product racemization occurring after the reaction, but simply to a moderate efficiency of catalyst **3a** in imparting enantioselection. To summarize, diluting the system has brought to an increase of the diastereoselectivity, while enantioselectivity has reached its maximum at intermediate concentration value.

Then, some solvents, belonging to different families, have been tested in optimized conditions, in order to understand if toluene was actually the right one and to see if it was possible to extend the feasibility of this reaction to different environments. In Table 9, results are described in terms of conversion and stereoselectivity, using, as usual, d.r. and e.e. as indicators.

Table 9



Entry	Solvent	Conversion (%)[a]	d.r.[a]	ee 4e-maj (%)[b]	ee 4e-min (%)[b]
AG086	Toluene	>99	1:22	65	-11
AG091	EtOAc	>99[c,f]	1:18	32	-33
AG092	THF	>99[d,g]	1:11	16	Rac
AG093	DCM	>99	1:5.2	14	6
AG094	Mixed Xylene	>99	1:21	62	Rac
AG095	Clorobenzene	>99	1:14	64	Rac
AG096	Trifluorotoluene	>99	1:4.6	50	Rac
AG097	Cyclohexane	>99[i,e,h]	1:4.8	Rac	Rac

Note: *NMR yield is no more reported, because internal standard solution has not been prepared for every solvent tested.*

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *Obtained after the addition of 1 equivalent of imine, absent in TLC check after 1h 30min of reaction.*

[d] *Obtained after the addition of 1 equivalent of imine, absent in TLC check after 4h 30min of reaction.*

[e] *Obtained after the addition of 1 equivalent of imine, absent in TLC check after 2h 30min of reaction at R.T.*

[f] *Reaction is carried out overnight*

[g] *Reaction is carried out for further three days.*

[h] *Reaction is carried out for further two hours.*

[i] *Due to system solidification, the reaction had to be moved to room temperature after half an hour.*

In the first place, it is possible to see see how diastereo- and enantioselection are not so strongly related to each other, confirming the assumptions already derived from concentration test (Table 8). Therefore, it is possible to distinguish among the checked solvents: those that positively have affected only d.r., those that, instead, have had a good influence also on e.e. and those that have not brought any improvement on the stereoselectivity.

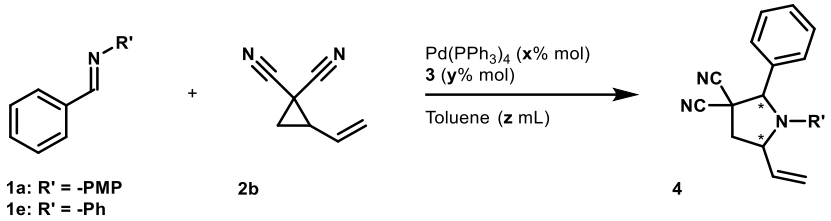
Starting from the most polar solvent (i.e. ethyl acetate), moving through tetrahydrofuran and dichloromethane, up to the less polar cyclohexane, it was possible to observe a sharp decrease in stereoselectivity, demonstrated by both d.r. and e.e. Nevertheless, while the enantiomeric enrichment is quite low since the beginning, THF and, even more, EtOAc have shown unexpected high values of diastereoselection, not so different from the reference (i.e. ***AG086***). However, due to the plausible presence of water interacting with their oxygen atoms, THF and ethyl acetate easily allow **1e** hydrolysis, carrying out benzaldehyde formation and the consequential need to add more imine to the system. Decomposition issues have been seen also in ***AG097***, but in that case, the unsuccessful results are attributed to the necessary raising in temperature, which, besides, greatly promotes epimerization mechanism, obtaining a racemic mixture of the products.

Finally, as expected, the best results are displayed by the use of aromatic compounds, as in ***AG094***, ***AG095*** and ***AG096***, that are the solvents more similar to the parent toluene. Despite the similarities, also among these three solvents, some differences are present. In fact, the strong EWG in trifluorotoluene decreased both d.r. and e.e. to values, reminding the unoptimized reaction with toluene (the one with the former dilution and catalysts ratio). On the contrary, EDG-substituted benzene and, in particular, xylenes have reached as good results as the ones shown by the optimized reaction with toluene (i.e. ***AG086***), however without overcoming it.

These results allow us to say that optimized conditions of the reaction are valid only using aromatic solvents and among them, only the less polar ones are really the best, such as toluene and xylene, for the lack of electron-donating or withdrawing groups that negatively effects stereoselectivity.

To further prove if all the work made in order to optimize this reaction mechanism, is actually valid only for the aforementioned substrates, the vinylcyclopropane **2b** was tested in place of **2d**.

Table 10



Entry	1	$Pd(PPh_3)_4$ loading (% mol)	3	3 loading (% mol)	Toluene volume (µL)	T (°C)	Conversion[a]
AG078	**1e**	5	**3z**	20	200	0	>99
AG084	**1e**	10	**3a**	5	200	-30	0
AG085	**1e**	10	**3b**	5	200	-30	0
AG088	**1e**	10	**3a**	5	200	0	0
AG089	**1e**	5	**3a**	10	200	-30	0
AG090	**1a**	10	**3a**	5	600[b]	-30	0

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

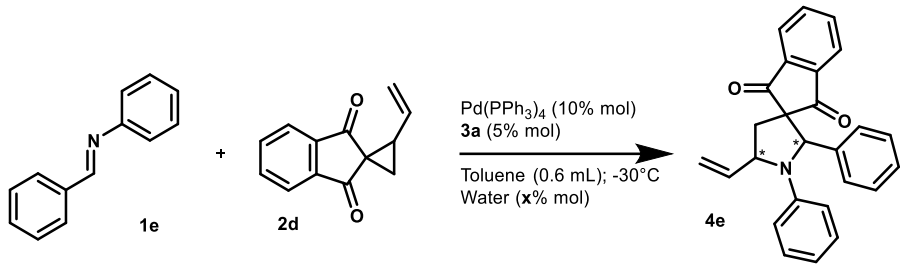
[b] *This quantity of toluene differs from the others because, meanwhile, this dilution is found to give the best results of stereoselectivity.*

While reaction went on straight with $(PhO)_2POOH$ (**3z**) in the initially used ratio with $Pd(PPh_3)_4$, there was no trace of product if chiral phosphoric acids (e.g. **3a**, **3b**) were employed with the theoretical optimal ratio. In order to understand which is the variable, between temperature and catalyst type and loading, that has brought the reactants to decomposition, two reaction where these parameters were restored to original conditions have been set up. Nevertheless, despite this effort, neither isolating the aforementioned variables any trace of the product has been shown in TLC or in NMR spectra. Therefore, imine **1a** was also tested in an optimized reaction with **2b**, since it was widely employed in previous conditions and it was discarded only because of the serious epimerization issues shown by the product. As further confirmation, even this reaction leads to reactants decomposition as much as the others, defining the ultimate specificity of the optimization made with vinylcyclopropane **2d** and imine **1e**.

It is possible to state these reactions seem to be reproducible, since the ones that gave the best results during the project, have been tested many times for this purpose. Despite this, some results are not exactly the same. Obviously, many changes could have been brought to the system, but one of the most difficult to control is the content of water in the solvent.

Therefore, in order to understand whether H_2O is involved somehow in reaction mechanism, affecting reactivity or stereoselectivity, three reaction with well-known content of water have been set up and results are reported in Table 11.

Table 11



Entry	Water content	Conversion (%)[a]	d.r. [a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG118	0 eq[c]	>99	1:11	64	-52
AG120	20 eq[c]	≈90	1:11	60	-68
AG121	Excess	>99	1:7	64	-47

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

[c] *Solvent was previously dried using pellets of 3Å molecular sieves.*

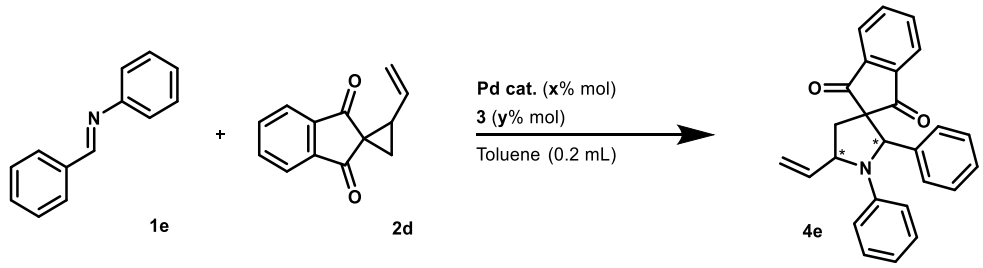
From data above, there does not seem to be a linear relationship between water content and conversion or stereoselection, since d.r. has the same value in anhydrous toluene and in the one where 20 equivalents of water have been added. Even more, the enantiomeric enrichment does not differ a lot in the reactions, as it is nearly identical between the one without water and that where toluene is saturated by H_2O. Hence, the hypothesis of the involvement of water in reaction mechanism, enhancing or weakening stereoselectivity, can be safely discarded.

3.4 Palladium source and ligands screening

Many works reported very good results when some chiral phosphine ligands are attached to a low-valent metal,[5,8,9,12] while in this project commercial $Pd(PPh_3)_4$ is the only metal complex used in the synergistic catalysis mechanism. Therefore, in order to test the feasibility of using this type of ligands also in these reactions, some different Pd sources and some phosphorous based ligands have been tested.

Initially, to understand if the aforementioned Pd sources were reactive by themselves, they have been employed without any ligand (Table 12).

Table 12



Entry	Pd cat.	Pd cat. loading (%mol)	3	3 loading (%mol)	T (°C)	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]
AG098	$Pd_2(dba)_3$	5	**3z**	20	R.T.	>99	64	1:1.3
AG099	$PdCl_2$	5	**3z**	20	R.T.	0	0	\
AG100	$Pd_2(dba)_3$	10	**3a**	5	-30[b]	≈15	15	1:1.9
AG101	$Pd(dba)_2$	10	**3a**	5	-30[b]	≈10	10	1:1.5

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

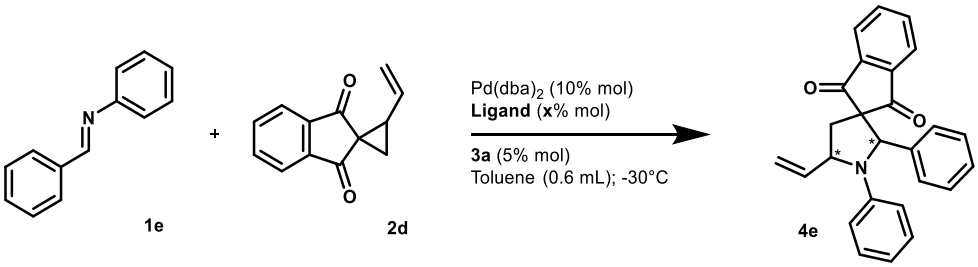
[b] *Reactions were kept at this temperature for 24h, then, as reactants were still there, they were moved to 0°C and finally to R.T. for further 8h.*

Firstly, the table above confirms the expected lack of reactivity in Pd(II) species, such as palladium chloride (***AG099***). In fact, only when the metal has valence 0, is able to undergo oxidative insertion in this kind of mechanisms[7,12] (see ***AG098***). Another evidence is the lowering in yield and conversion displayed by $Pd(dba)_2$ and its dimer, when they were used in the optimized conditions (see ***AG100*** and ***AG101***). This feature could be useful if you want that only the metals coordinated by chiral ligands play their role in the reaction.

Then, the procedure described in section 5.5 has been modified in order to test ligands effect on system reactivity. The proper quantity of $Pd(dba)_2$ (10% mol) and ligands were

dissolved by 300 µL of toluene in a vial, kept under stirring for 30 minutes. After that, the content has been transferred into another vial, where imine **1e**, vinylcyclopropane **2d** and phosphoric acid **3a** (5% mol) had already been dissolved in the same volume of toluene and stirred at -30°C, with respect to optimized conditions (temperature, dilution, catalysts ratio).

Table 13



Entry	Ligand	Ligand loading	Conversion (%)[a]	NMR Yield (%)[a]	d.r.[a]
AG102	BINAP	12% mol	≈85[b]	75	1:3.7
AG103	DPPE	12% mol	≈35[b,c]	6	\
AG107	DPPP	20% mol	0	0	\
AG108	DPPB	20% mol	>99[d]	29	1:4.0
AG109	BINAP	20% mol	≈85[d]	32	1:2.2

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *After 3h, there was no conversion. Then, system has been moved to R.T. and kept reacting for further 20h.*

[c] *An equivalent quantity of the initial Pd(0) and DPPE, dissolved in further 0.3 mL, was added after 3h.*

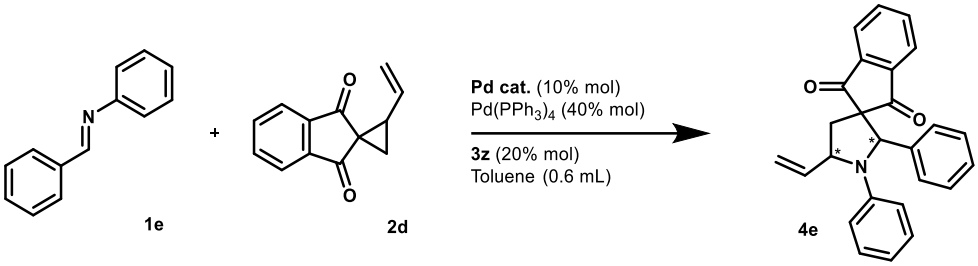
[d] *After two days, there was no conversion. Then, system has been moved to R.T. and kept reacting for further 20h.*

None of the tested ligand has brought positive effects to the reaction, which in some cases has reached almost full conversion, but it never did it at -30°C, where epimerization mechanism is thwarted by kinetic. Therefore, the results represented above show a really bad stereoselectivity, in terms both of d.r. and even more of enantiomeric enrichment, that, in fact, is not reported, as every reaction gave racemic products.

Comparing ***AG109*** to ***AG102***, the lowering in yield and in diastereoselection could be due to the loading of BINAP, that, hindering the metal centre of the coordination compound, decreases the interaction between the active Pd and the substrate.

In order to understand if the problem displayed by these results has to be ascribed to ligand exchange or it is due to the effective activity of the formed complexes, it has been substituted with triphenylphosphine (40% mol), since $Pd(PPh_3)_4$ has always shown itself as good source of palladium(0) in oxidative addition mechanism for 1,3-dipole formation.

Table 14



Entry	Pd cat.	T (°C)	Conversion (%)[a]	d.r.[a]
AG104	$Pd_2(dba)_3$	-30	>99	1:6.4
AG105	$Pd(dba)_2$	-30	>99	1:7.4
AG106	$PdCl_2$	R.T.	≈15[b]	1:0.2

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *This value is obtained reacting overnight at R.T., then 6h at 60°C and finally 1h at 90°C.*

The most interesting data of the table above regards the conversion displayed by ***AG104*** and ***AG105***, whose value means that the problems of reactivity and stereoselectivity, reported in Table 13, are probably related to the so-obtained palladium complexes activity, rather than to the procedure used to exchange the ligand.

4 CONCLUSIONS

From the results obtained during this project, it is possible to assert that a new catalytic enantioselective reaction between vinylcyclopropanes (VCP) and imines is feasible exploiting the synergistic combination of palladium catalyst and chiral phosphoric acids.

Among the studied substrates, those that seemed to be more promising are the VCP **2d** and the imine **1e**, due to their high reactivity and the possibility to characterize the product obtained by them, which displayed two diastereomeric couples that could be identified by NMR, purified by chromatography and analysed by chiral stationary phase HPLC.

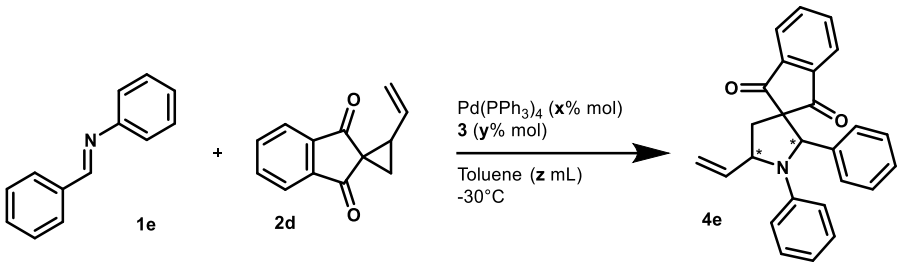
Then, it has been discovered that $Pd(PPh_3)_4$ was the only palladium(0) source that activates efficiently vinylcyclopropanes, forming formal 1,3-dipole, while other sources are not so effective in doing that, even if the metal is coordinated by phosphine ligands, such as DPBE or BINAP.

The first optimization experiments have shown that, although many chiral phosphoric acids were able to activate the imines and induce stereoselectivity in the products, CPA **3a** is the one that has given the most promising results, leading to higher diastereo- and enantioselectivity results in comparison with the other ones tested in the same conditions, reaching a d.r. of 1:3.20 and an ee of the major diastereoisomer of almost 42%.

Then, one of the most important part in the development of the synergistic mechanism of these reactions has been found to be the tuning of the ratio between the palladium complex and the phosphoric acid, because moving from 1:2 to 2:1 respectively (10% mol of $Pd(PPh_3)_4$ and 5% mol of **3a**), has brought to the highest improvement in the enantioselectivity studied by this project, raising the enrichment by almost 20 percentage points for the major diastereoisomer (60% ee). In addition, the d.r. increased considerably, reaching the value of 1:7, more than doubling the one obtained with the previous catalysts loading.

The last crucial step in the optimization of the synergistic catalysis described in this work, was the dilution of the system, which has found its optimum when reactants and catalysts were dissolved in 600 µL of toluene, at 0.050 mmol scale, where diastereomeric ratio has reached the impressive value of 1:22 and the enantiomeric excess increased to 65% with respect to the major diastereoisomer couple. This optimization pathway is summarized in Table 15.

Table 15



Entry	Optimized variable	Conversion (%)[a]	NMR Yield (%)[a]	d.r. [a]	ee 4e maj (%)[b]	ee 4e min (%)[b]
AG040	**3a** catalyst	>99	81	1:3.2	42	11
AG060	Pd:PA **10:5**	>99	66	1:7.0	60	35
AG086	Dilution **600 µL**	>95	79	1:22	65	-11

[a] *Calculated by ^{1}H-NMR spectroscopic analysis made on the crude mixture of reaction.*

[b] *Calculated by HPLC after purification by chromatographic column.*

Although these results are reproducible, higher values of enantioselectivity were not reached in this work. In fact, the use of drying agents did not improve the reaction selectivity, since the presence of water in the solvent does not seem to affect yield or stereoselectivity. Similarly, not even using different solvents has seemed to improve these parameters, as good results were obtained only by aromatic compounds as toluene and xylene.

The hope of enhancing the enantioselectivity is to find another chiral catalyst able to impart more geometric definition to the transition state of the reaction. Otherwise, the goal would be to succeed in coordinating some chiral ligands to a suitable palladium(0) source in order to make the activation of the VCP driven by a chiral auxiliary as much as the one of the imine, controlled by the axial chirality of the phosphoric acid.

5 EXPERIMENTAL

5.1 General materials, instrumentation and methods

Unless otherwise specified, solvents and reactants used for the preparation of substrates (5.2, 5.3) and catalysts (5.4) are commercially available.

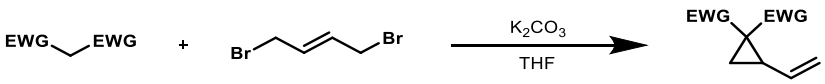
The advancement of reactions has been monitored by TLC, and every crude or purified sample has been characterized by ^{1}H-NMR (Varian® AS 300 and 400 spectrometers) in $CDCl_3$ as deuterated solvent. The so obtained spectra are reported on ppm scale, and the chemical shifts are calibrated from chloroform signal set at 7.26 ppm. NMR yields has been determined using bibenzyl as internal standard.

The products have been also characterized by HPLC (Varian® Prostar), using Daicel® chiral stationary phase columns.

Chromatographic purification has been performed, in different columns and proper eluent mix, but always with silica gel as stationary phase (70-230 mesh).

The solvents have been eliminated by using rotary evaporator, high vacuum pump after reaction and purification, and stripped by N_2 flow after products removal from flasks or NMR tubes.

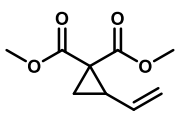
5.2 General procedure for synthesis and characterization of Vinylciclopropanes[13]



One equivalent of a C-H acidic compound and one of 1,4-dibromobut-2-ene were weighted and added to a 250 mL round bottom flask, where a magnetic stirring bar has been already inserted. To this, THF was added, dissolving the reactants and making a 0.2 M solution. Then, also 2.5 equivalents of K_2CO_3 were added, obtaining a suspension, due to the low solubility of the carbonates in organic environment. For this reason, the stirring bar had to move very fast (more than 600 rpm), preventing the insoluble powder to settle on the bottom of the flask, inhibiting the reactivity. After this, a condenser was applied, and reaction mixture has been heated to 60°C with a thermostatic oil bath and left to reflux overnight. The morning after, the reaction was checked by TLC, in order to see if reactants signals were disappeared, while the one of the product is visible (the match was made comparing the crude with the same purified product previously obtained), indicating full conversion. Then, the flask was brought to R.T., and then reaction mixture was filtered over a celite pad on a Gooch funnel, on a tailed flask linked to a vacuum pump, for

carbonate removal, and everything was washed with Et_2O, in order to collect as much product as possible. Hence, the organic phase was poured in a separating funnel with an approximately equivalent volume of a saturated aqueous solution of $NaHCO_3$, the so obtained bi-phasic system was gently shaken for avoiding the formation of a stable emulsion. Once the separation has been complete, the organic phase was washed again with a NaCl aqueous saturated solution, but the funnel was shaken more vigorously, because the risk of producing an emulsion was much lower in this case. The organic phase, obtained at the end of these treatments, was dried by the addition of $MgSO_4$, filtered again over a Gooch funnel for drying agent removal and then concentrated by rotary evaporation and the help of high vacuum pump for NMR check. The crude product was purified by chromatographic column with proper eluent mix, as described in the sections below.

5.2.1 Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (**2a**)

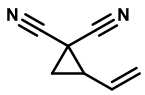


The crude product was obtained, according to the procedure described in the previous paragraph, from dimethylmalonate (10 mmol, 1.32 g) and 1,4-dibromobut-2-ene (10 mmol, 2.14 g). Hence, it was purified by chromatographic column using an eluent mix composed by hexane and ethyl acetate in 1:1 ratio, giving a 31% yield.

Rf = 0.40 (hexane / ethyl acetate 1:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.53-5.36 (m, 1H), δ 5.35-5.24 (m, 1H), δ 5.13 (dd, J = 8.5, 1.3 Hz, 1H), δ 3.76 (s, 6H), δ 2.62-2.54 (m, 1H), δ 1.71 (dd, J = 7.3, 4.8 Hz, 1H), δ 1.60 (dd, J = 9.1, 4.8 Hz, 1H) ppm.

5.2.2 2-vinylcyclopropane-1,1-dicarbonitrile (**2b**)

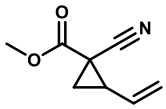


The crude product was obtained, according to the procedure described in 5.2 paragraph, from malonitrile (10 mmol, 0.66 g) and 1,4-dibromobut-2-ene (10 mmol, 2.14 g). Differently from the aforementioned procedure, 2 g of potassium carbonate were added after 18 hours. Then, the reaction ran for two more hours before being worked up. Hence, it was purified by chromatographic column using an eluent mix composed by petroleum ether and ethyl acetate in 6:1 ratio, giving a 43% yield.

Rf = 0.30 (petroleum ether / ethyl acetate 6:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.72-5.47 (m, 3H), δ 2.73-2.63 (m, 1H), δ 2.11-2.03 (m, 1H), δ 1.86-1.79 (m, 1H) ppm.

5.2.3 Methyl 1-cyano-2-vinylcyclopropane-1-carboxylate (**2c**)

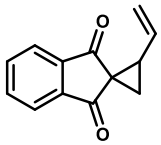


The crude product was obtained, according to the procedure described in 5.2 paragraph, from methyl 2-cyanoacetate (15 mmol, 1.49 g) and 1,4-dibromobut-2-ene (15 mmol, 3.21 g). Hence, it was purified by chromatographic column using an eluent mix composed by petroleum ether and ethyl acetate in 5:1 ratio, giving a 63% yield. The product was obtained as a single diastereoisomer.

Rf = 0.25 (petroleum ether / ethyl acetate 5:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.70-5.53 (m, 1H), δ 5.45-5.31 (m, 2H), δ 3.79 (s, 3H), δ 2.64-2.48 (m, 1H), δ 1.98-1.92 (m, 1H), δ 1.67-1.60 (m, 1H) ppm.

5.2.4 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione (**2d**)

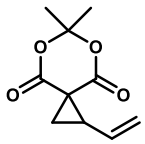


The crude product was obtained, according to the procedure described in 5.2 paragraph, from indene-1,3-dione (15 mmol, 2.19 g) and 1,4-dibromobut-2-ene (15 mmol, 3.21 g). Hence, it was purified by chromatographic column using an eluent mix composed by petroleum ether and diethyl ether in 6:1 ratio, giving a 33% yield.

Rf = 0.40 (petroleum ether / diethyl ether 6:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.98-7.90 (m, 2H), δ 7.83-7.76 (m, 2H), δ 6.10-5.96 (m, 1H), δ 5.30 (dd, J = 17.1, 1.1 Hz, 1H), δ 5.15 (dd, J = 10.4, 1.4 Hz, 1H), δ 2.82 (dd, J = 17.5, 8.7 Hz, 1H), δ 2.14 (dd, J = 8.7, 3.9 Hz, 1H), δ 1.99 (dd, J = 8.7, 3.9 Hz, 1H) ppm.

5.2.5 6,6-dimethyl-1-vinyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**2e**)

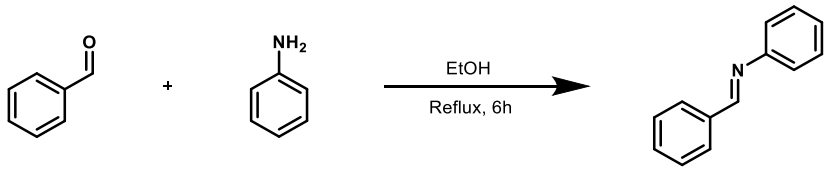


The synthesis of the title product differs a little from the one described in the previous section, due to compound higher sensitivity. 1.44 g of Meldrum's acid (10 mmol) and 1.7 g of potassium carbonate (12.5 mmol) were suspended in 10.20 mL of DMF and stirred at 0°C for 10 minutes, after which 2.57 g of 1,4-dibromobut-2-ene (12 mmol) were added and the reaction stirred for 1h at 0°C and 2h at room temperature. A further portion of K_2CO_3 (1.7 g, 12.5 mmol) was added and the reaction was stirred for 21 hours, after which it was poured into a large excess of a 1M aqueous HCl solution. The obtained mixture was added to a separating funnel and extracted six times with EtOAc (about 60 mL). To this bi-phasic system, 60 mL of saturated NaCl aqueous solution and others 60 mL of pure water were added. The organic layer was dried by $MgSO_4$, filtered and concentrated by rotary evaporator and high vacuum pump for NMR

check. The crude product was purified by chromatographic column using an eluent mix composed by petroleum ether and Et_2O in 2:1 ratio, giving a yield of 35%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.85-5.79 (m, 1H), δ 5.46 (dd, J = 17.1, 1.1 Hz, 1H), δ 5.34 (dd, J = 10.6, 1.1 Hz, 1H), δ 2.77 (dd, J = 9.2, 9.2 Hz, 1H), δ 2.37 (dd, J = 9.2, 4.7 Hz, 1H), δ 2.22 (dd, J = 8.7, 4.7 Hz, 1H), δ 1.77 (s, 3H), 1.73 (s, 3H)

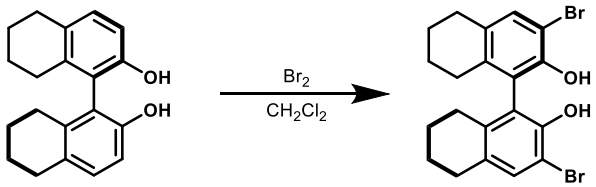
5.3 Synthesis and characterization of N,1-diphenylmethanimine[14] (**1e**)



1.6 mL of benzaldehyde (15 mmol) were added to a 100 mL round bottom flask containing 30 mL of a 0.5 M ethanol solution of aniline (15 mmol) and equipped with a magnetic stirring bar. The reaction mixture has been held under reflux (T>70°C) for 6 hours and then, after complete conversion, confirmed by the absence of the aniline signals in TLC and NMR analysis. The crude product, obtained by spontaneous crystallization at room temperature, was filtered by Buchner funnel and washed by a little amount of hexane. Heating and cooling have been avoided, in order to give a higher crystals purity grade, as it can be seen in NMR spectrum and a yield that reaches 53%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.47 (s, 1H), δ 7.96-7.89 (m, 2H), δ 7.53-7.46 (m, 3H), δ 7.45-7.36 (m, 2H), δ 7.28-7.19 (m, 3H) ppm.

5.4 Synthesis and characterization of Chiral Phosphoric Acid Catalyst[15,16] (**3a**)

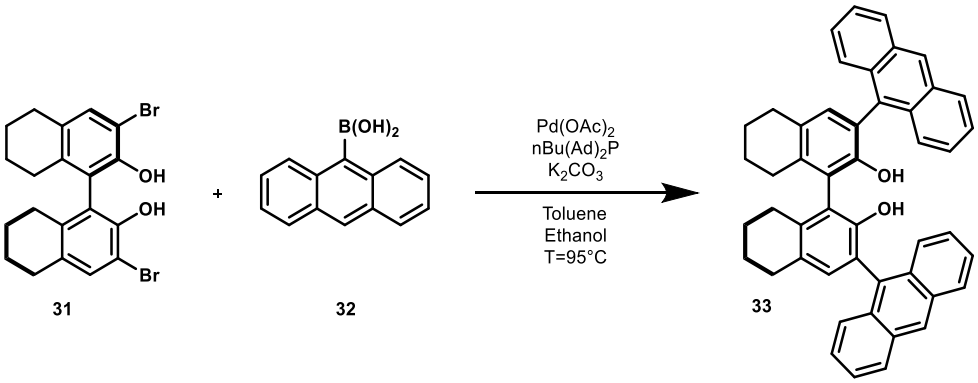


30 **31**

0.99 g of the compound **30** (3.35 mmol of H_8-BINOL), obtained from a previous hydrogenation of the commercial binaphtol are dissolved in 18.42 mL of dichloromethane in a 100 mL round bottom flask, equipped with a magnetic stirring bar. The vessel was kept under nitrogen flow into a liquid N_2 and EtOH bath, which temperature was -30°C, while 400 µL of Br_2 were added on it drop by drop. The reaction was quenched after half an hour with the aid of 16.45 mL of a saturated aqueous solution of $Na_2S_2O_5$, reducing the molecular bromine to bromide. The reaction mixture was inserted in a separating funnel

and washed by brine and DCM, so, after shaking, the organic phase was collected in another flask, where it has been concentrated with rotary evaporation, and then purified by chromatographic column eluted with a 4:1 mix of hexane and diethyl ether, obtaining a yield of 63%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 2H), δ 5.11 (s, 2H), δ 2.81 (t, J = 4.3 Hz, 4H), δ 2.36-2.26 (m, 2H), δ 2.17-2.07 (m, 2H), δ 1.79-1.66 (m, 8H) ppm.

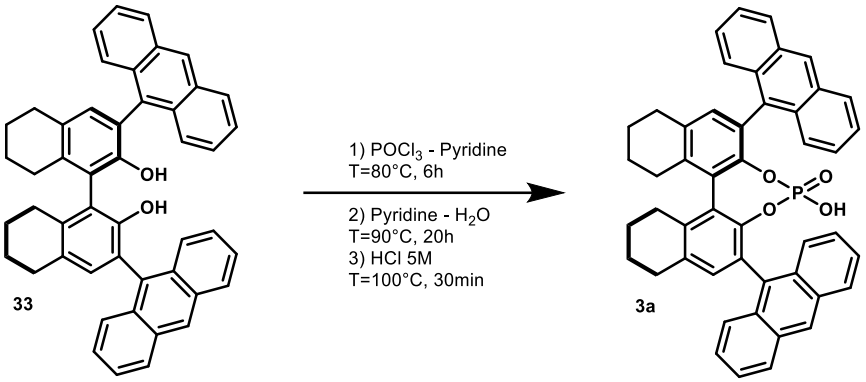


31 32 33

The obtained brominated compound **31** (0.40 g, 0.88 mmol) was put in a Schlenk tube, previously linked to a high vacuum pump and heated to remove possible traces of water, with 4.1 equivalent of boronic acid **32** (0.80 g, 3.61 mmol), 0.1 eq of palladium acetate (19.8 mg, 0.088 mmol), 0.11 eq of the hindered phosphine ligand $nBu(Ad)_2P$ (34.7 mg, 0.097 mmol), 20 eq of potassium carbonate (2.50 g, 18.05 mmol) and a magnetic stirring bar under nitrogen flow. A mixture of 10 mL of toluene and 2.5 mL of ethanol, degassed by a 30 minutes insufflation of N_2, was poured in the vessel under nitrogen flow. Therefore, the tube has been sealed, inserted in a pre-warmed oil bath at the regulated temperature of 95°C and kept in it for 20 hours. Having checked by TLC that the reaction had taken place, the vessel was brought to room temperature and, washed by 50 mL of ethyl acetate, the organic phase was transferred in a separating funnel with 70 mL of a saturated aqueous solution of ammonium chloride. The layers were separated and the aqueous phase was washed three times with 50 mL of DCM each. Hence, the organic extracts were collected and dried over $MgSO_4$, then filtered through a Gooch funnel in a round bottom flask, which content was concentrated by rotary evaporation. The crude product was purified by chromatographic column using an eluent mix composed by hexane and dichloromethane in an initial ratio of 2:1, then brought to 1:1 when the signal with the highest Rf was no longer visible, obtaining pure compound **33**, confirmed by NMR spectrum, with a 28% yield.

Rf = 0.45 (Hexane / DCM 2:1)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 2H), δ 8.12-8.00 (m, 4H), δ 7.89-7.82 (m, 2H), δ 7.76-7.68 (m, 2H), δ 7.55-7.47 (m, 4H), δ 7.47-7.39 (m, 2H), δ 7.34-7.25 (m, 2H), δ 7.10 (s, 2H), δ 4.62 (br s, 2H), δ 2.90-2.80 (m, 4H), δ 2.80-2.57 (m, 4H), δ 2.00-1.83 (m, 8H) ppm.



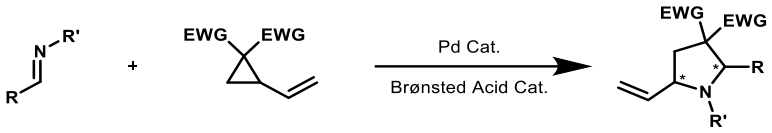
In a 100 mL round bottom flask, equipped with a magnetic stirring bar, 0.35 g of the compound **33** (0.54 mmol) were inserted and dissolved in 1 mL of pyridine (dried over 3Å molecular sieves). Then, a solution of 100 µL of $POCl_3$ dissolved in another one mL of the same dried pyridine has been added dropwise to the previous one. Hence, the vessel is linked to nitrogen flow and inserted in a thermostatic oil bath at the temperature of 80°C for 3h 30min, after which an equivalent quantity of the aforementioned $POCl_3$ solution was added, and the mixture is vigorously stirred for other 2h 30min. The crude has been checked by TLC (hexane/DCM 1:1 and hexane/EtOAc 4:1) and, when there was no longer trace of **33** signal, the flask was brought to room temperature. To that, 10 mL of pyridine and 17 mL of water were added and the vessel was linked to a condenser and heated to 90°C for 20 hours. Therefore, after cooling to room temperature, 30 mL of a 5M HCl solution has been prepared by using 12.5 mL of concentrated hydrochloric acid (37% m/m) diluted in distilled water. This solution was carefully added to reaction mixture, heated to 100°C and stirred for 30 minutes. After cooling again to room temperature, the flask content was transferred to a separating funnel with the aid of 100 mL of CH_2Cl_2 and 100 mL of water. After shaking, the phases were separated and the aqueous one was extracted twice with the same amount of dichloromethane. The organic phases were collected and dried over magnesium sulphate, filtered through a Gooch funnel in a round bottom flask and concentrated by rotary evaporation. The crude product was purified by chromatographic column, prepared with dichloromethane, then eluted with a mixture of DCM and MeOH, that goes from 99:1 to 95:5 ratio, until there are product traces. The so

obtained pure product was treated as the crude one (HCl quenching and CH_2Cl_2 extraction) in order to obtain compound **3a**, filtered and dried, giving 81% yield.

Rf = 0.50 (DCM / MeOH 95:5)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 2H), δ 7.87 (d, J=8.4 Hz, 2H), δ 7.77 (d, J=8.4 Hz, 2H), δ 7.67 (d, J=8.1 Hz, 2H), δ 7.59 (d, J=8.1 Hz, 2H), δ 7.43-7.31 (m, 4H), δ 7.29-7.16 (m, 4H), δ 7.11 (s, 2H), δ 4.80 (br s, 3H), δ 3.12-2.98 (m, 2H), δ 2.98-2.85 (m, 4H), δ 2.77-2.61 (m, 2H), δ 2.13-1.82 (m, 8H) ppm.

5.5 General procedure for synthesis and characterization of chiral pyrrolidines[5,7,8,12]

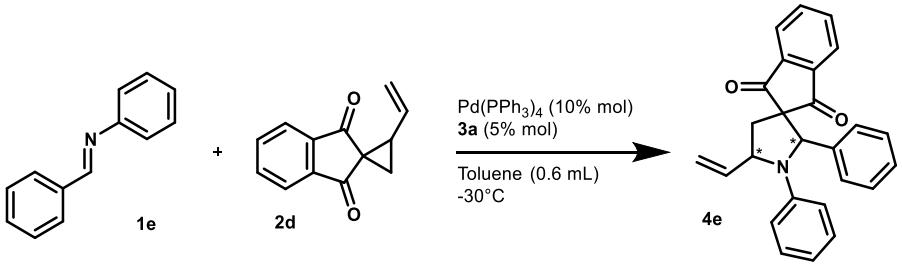


1.1 equivalent of imine, 1.0 of vinylcyclopropane and a Brønsted acid catalyst were sequentially added to a screw-capped vial (or a Schlenk for reactions under nitrogen). The compounds were dissolved in a solvent and a magnetic stirring bar was added to the mixture, which is then stirred for some minutes in the requested conditions. Palladium catalyst was then added and, since then, the reaction has been ran until complete conversion of the VCP (TLC check).

The crude product was filtered by a little silica plug, washed by ethyl acetate and, after being concentrated, has been analysed by NMR spectroscopy.

Then, it was purified by chromatographic column with a mixture of petroleum ether and ethyl acetate in a 4:1 ratio, after which it was concentrated again and, dissolved in DCM, it has been transferred into a vial filled by an equipollent mixture of isopropanol and hexane, which content was injected in a chiral stationary phase HPLC column. The obtained chromatogram has allowed calculating the enantiomeric enrichment between diastereoisomer couples.

5.6 Optimized procedure for synthesis and characterization of chiral pyrrolidines



10.0 mg of N,1-diphenilmethanimine (0.055 mmol), 10.0 mg of 2-vinylspiro[cyclopropane-1,2'-indene]-1',3'-dione (0.050 mmol) and 1.7 mg chiral phosphoric acid **3a** ($2.5 \cdot 10^{-3}$ mmol), as obtained by the procedure described in sections 5.2.4, 5.3 and 5.4 respectively, were sequentially added to a screw-capped vial. The compounds were dissolved in 600 µL of a toluene solution, containing 2.28 mg of bibenzyl (0.0125 mmol) used as internal standard for NMR yield calculation (δ 2.95 ppm – ^{1}H-NMR, 300 MHz, $CDCl_3$). After the addition of a magnetic stirring bar, the mixture was stirred for some minutes at -30°C in a thermostatic ethanol bath, while 6.0 mg of $Pd(PPh_3)_4$ ($5.0 \cdot 10^{-3}$ mmol) has been weighted. The organometallic catalyst was then added to the vial, which it has been kept at the aforementioned temperature for about 1h 30min, when complete conversion was reached, as confirmed by TLC check (disappearance of VCP signal). Purification and characterization were made according to the procedure described in section 5.5. A Daicel® OD-H chiral stationary phase column and a mixture of hexane and isopropanol in a 95:5 ratio are employed in order to determine the enantiomeric excesses of the two diastereoisomers by HPLC: retention time of the peaks in these condition (flow = 0.75 mL/min; λ = 254 nm) are: 9.83 (major enantiomer) and 10.54 min (minor enantiomer) for the first enantiomers couple (major diastereoisomer), while 11.90 (minor enantiomer) and 14.80 min (major enantiomer) for the latter (minor diastereoisomers).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.01-7.55 (m, $4H_{maj}$, $4H_{min}$), δ 7.24-7.17 (m, $1H_{maj}$, $1H_{min}$), δ 7.16-6.88 (m, $6H_{maj}$, $6H_{min}$), δ 6.76-6.50 (m, $3H_{maj}$, $3H_{min}$), δ 6.41 (ddd, J = 17.5, 10.4, 7.4 Hz, $1H_{min}$), δ 5.82 (ddd, J = 17.5, 10.5, 7.4 Hz, $1H_{maj}$), δ 5.53-5.19 (m, $4H_{maj}$, $2H_{min}$), δ 4.95 (s, $1H_{min}$), δ 4.82 (q, J = 7.5 Hz, $1H_{min}$), δ 2.60-2.31 (m, $2H_{maj}$, $2H_{min}$) ppm.

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