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Asymmetric synthesis of 1,n diamines

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Parole chiave: Ring closing metathesis, 3,6-Disubstituted 1,2-Diaminocyclohexanes, 2,5-diazabicyclo[2.2.1]heptanes, Unsaturated δ-Substituted δ-Lactams, Asymmetric allylic alkylation, DIAZAP ligands.

Gennaio 2004-Dicembre 2006

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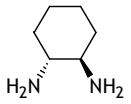
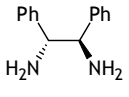
Chapter 1
Introduction

1.1. Importance and use of chiral 1,2 diamines.

The 1,2-diamino moiety is present in many chiral natural products with valuable biological properties and in drugs where the pharmacological activity is related to their absolute configuration. Moreover, enantiopure 1,2-diamines are widely used as chiral auxiliaries and ligands in asymmetric synthesis and catalysis, especially the C_2-symmetric *trans*-1,2-diaminocyclohexane **1** and *syn*-1,2-diphenyl-1,2-diaminoethane **2** and their *N*,*N*'-disubstituted derivatives[1].

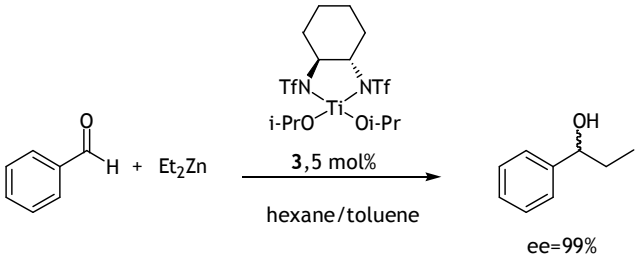


1



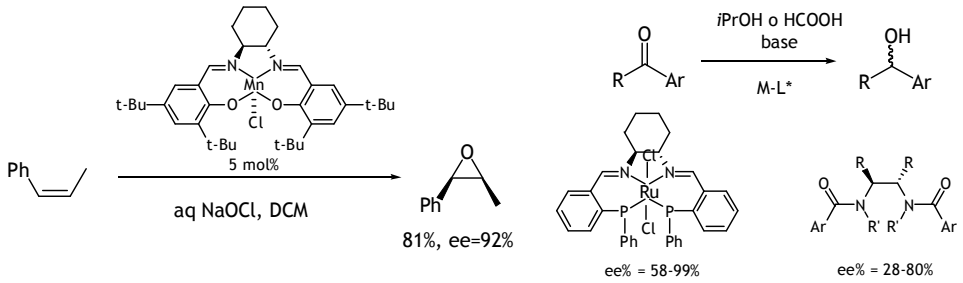
2

For example the titanium complex **3** can promote the addition of diethylzinc to aromatic aldehydes with high control of enantioselectivity. The same reaction protocol has been extended further to aliphatic aldehydes[2].

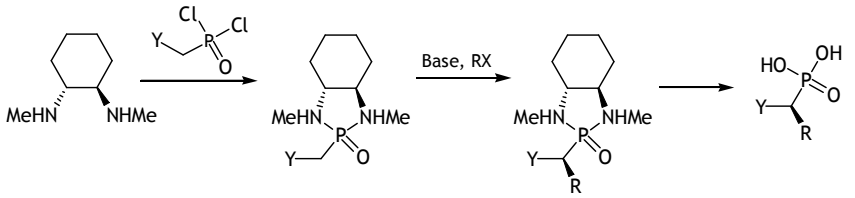


ee=99%

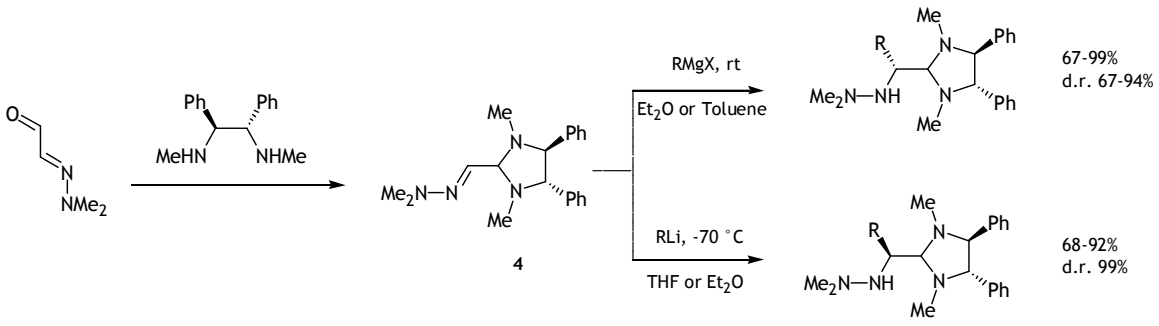
Moreover, *trans*-1,2-diaminocyclohexane is the source of chirality in metal-salen complexes which are a class of "privileged" ligands that are able to catalize in an enantioselective fashion a great variety of reaction like, for example the epoxidation of olefins[3] or the reduction of prochiral chetones[4].



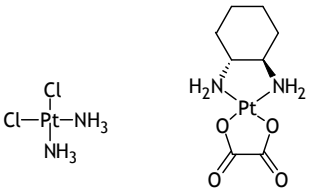
These compounds have been used also as chiral auxiliaries for the synthesis of enantiopure compounds; for example Hanessian employed *trans*-1,2-diaminocyclohexane to prepare chiral α-alchil-substituted phosfonic acids[5].



Alexakis and Mangeney studied cyclic aminals derived from N,N'-dimethyl-1,2-diphenyl-1,2-diaminoethane as chiral auxiliaries in the addition of organometallic reagents to hydrazone **4**. Very good control of diastereoselectivity was generally obtained, but the addition of Grignard reagents followed the opposite sense of asymmetric induction with respect to organolithium reagents[6].

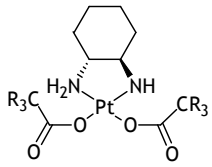


These compounds are also very important for their pharmacological properties. In fact, a large set of biologically active compounds feature the 1,2-diamino moiety. For example, the *cis*-platinum complex **5** and its derivatives **6** and **7** are active as anticancer agents[7a].



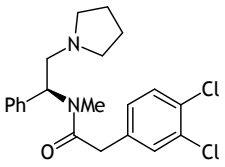
Cis-Platinum
5

Oxalyl-Platinum
6



NDDP
7

Compounds **8** and **9** showed a powerful agonist effect for the κ–opioid receptor and show low effects of dependency and other collateral effects[7b].



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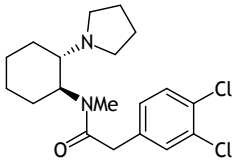
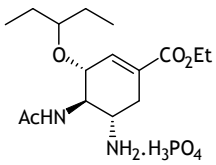


9

Tamiflu™ is an anti-influenza drug developed by Roche and has recently received attention as a possible defence against the outbreak of the avian flu.[8]



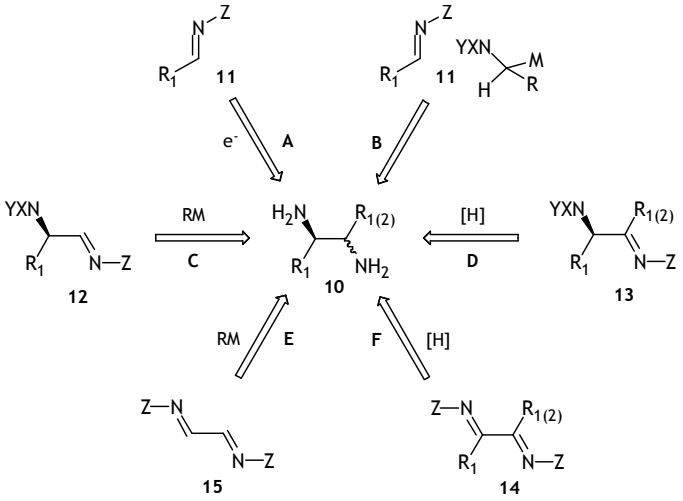
Tamiflu™

1.2. Asymmetric synthesis of 1,2 diamines from chiral imines.

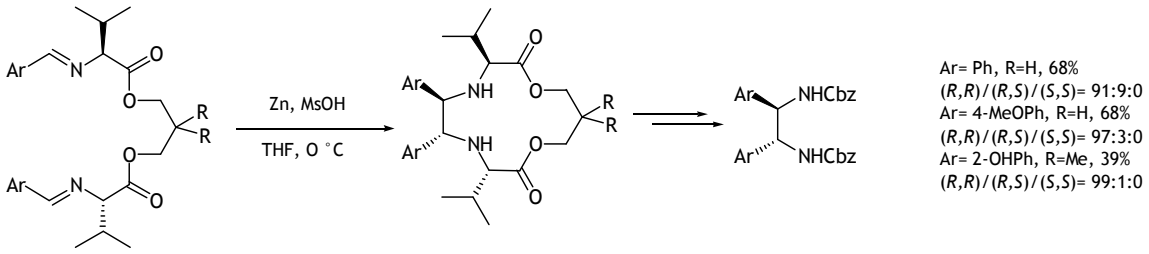
For the above reported reasons, the synthesis and chemistry of 1,2-diamines[9,10] attracted very much interest in the past and many synthetic routes to these compounds from different functional groups have been described. On the other hand, many optically pure compounds are available from the "chiral pool" and can be used as starting materials for the preparation of properly designed, optically pure 1,2-diamines. Im this case, the existing stereocenter(s) can be maintained, or a new stereocenter(s) can be created exploiting the asymmetric induction of the already present one(s). Such asymmetric transformations have been increasingly employed in the last few decades, as an alternative

to optical resolution[9,11,12] and enzyme-catalyzed kinetic resolution[13-15], which are principally based on the use of optically pure monocarboxylic and dicarboxylic acids.

1,2-Diamines with general structure **10** can be synthesized from precursors containing one or two prochiral azomethine functions (C=N), involving in the first step the stereoselective formation of one or two stereocentres in the ethylene tether linking the two nitrogen atoms (Scheme). To obtain the primary 1,2-diamines, the nitrogen substituent *Z* has to be removed in a subsequent step by using methodologies which must not affect the stereochemical integrity of the intermediate compounds. For example, route A involves the stereoselective formation of the C1–C2 bond by the reductive coupling of monofunctional compounds **11**. This occurs by a preliminary single electron transfer from an electrode or a chemical reductant species, and is generally suited to the preparation of symmetrically 1,2-disubstituted 1,2-diamines **10** ($R^1 = R^2$). Also, the addition of an α-aminoalkyl metal reagent to monoazomethine compounds **11** leads to the same target **10** (route B). On the other hand, routes C–F exploit transformations of unsaturated compounds already possessing the N–C–C–N skeleton. In fact, in routes C and D the chiral α-amino azomethine compounds **12** and **13**, arbitrarily depicted with the *R* configuration, undergo addition by an organometallic reagent and a reducing agent (hydrogen, hydride), respectively. Finally, symmetrically or unsymmetrically 1,2-disubstituted 1,2-diamines **10** can be obtained by the analogous reactions of 1,2-bis(azomethine) compounds, like 1,4-diazadienes **14** and **15** (routes E and F). The reactivity of the azomethine compound and consequently the applicability of a given methodology and/or the choice of the reagent are dependent on the nature of both the C- and the N-substituents (imine, oxime, hydrazone, nitrone). These methods are complementary to other ones which exploit the addition of nitrogen compounds to C=C bonds[9,16].

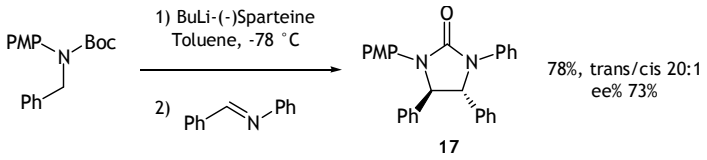


For example, Kise described the reductive coupling (route A) of aromatic imines derived from valine esters, but good diastereoselectivity was obtained only when a tether between the two imine functionalities was present like in **16**[17].



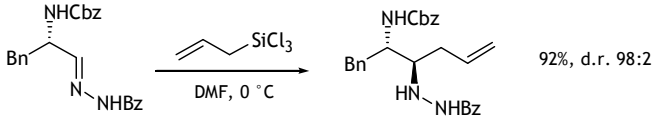
16

Boys proposed a synthesis of the chiral cyclic urea **17** that features the addition of chiral α-amino carbanions, obtained by asymmetric hydrogen abstraction (metallation) of N-benzylic amides by the BuLi-(-)-sparteine complex to imines (route B)[18].



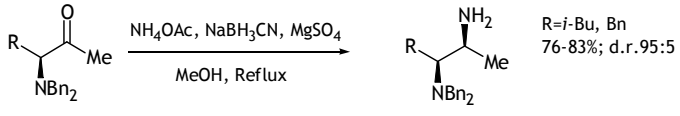
17

The addition of organometallic reagents to α–amino imines is a widely exploited route since these compounds are widely available from the corresponding α–aminoacids (Route C). Kobayashi studied the addition of allyltrichlorosilane to the chiral α-amino-hydrazone **18,** which proceeded with high yield and good control of diastereoselctivity[19].



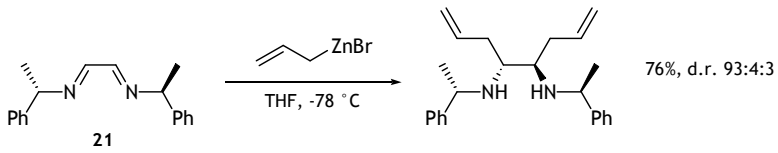
18

The reduction of α–amino ketimines is complementary to the organometallic addition to aldimines. As described by Reetz, the chiral 1,2 diamine **20** was synthesised by reductive amination of the chiral α–amino-ketone **19** (Route D)[20].

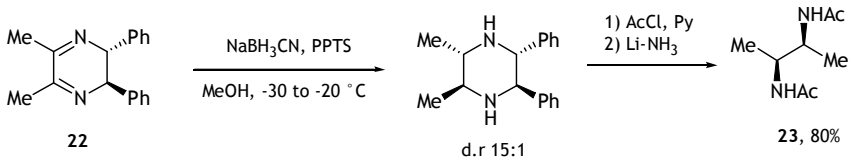


19 **20**

Our research group has been very active in the enantioselective synthesis of this class of compounds by addition of organometallic reagents to the chiral 1,2-*bis*-imine derived from glyoxal and 1-phenylethylamine as chiral auxiliary **21** (route E). For example, allylzinc bromide reacted at low temperature with very high control of diastereoselectivity. The main diastereoisomer was obtained pure by crystallization from MeOH with 76% yield[21].



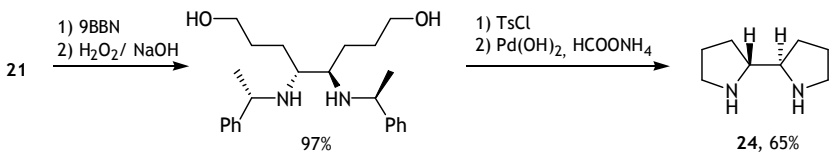
The reduction of chiral 1,2-*bis*-imines has been also exploited (Route F), e.g. the reduction of the chiral dihydropyrazine **22** is the key step of the asymmetric synthesis of **23**[22].



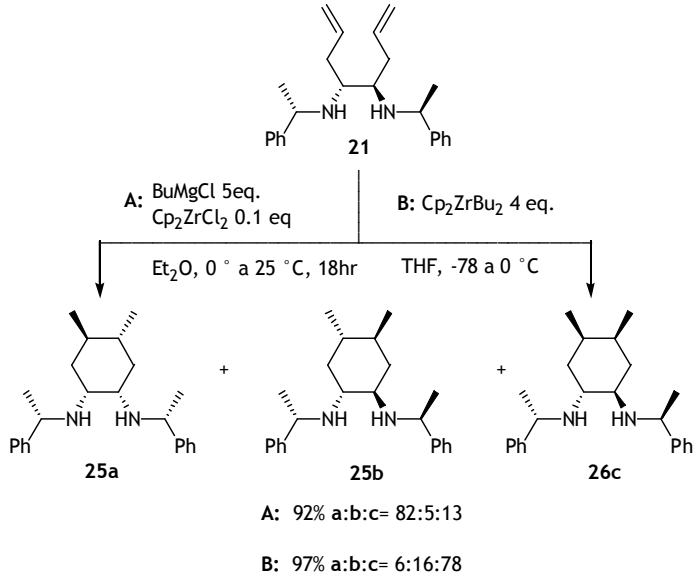
1.3. Homoallylic amines as precursors of cyclic amines

Enantiopure homoallylic amines are valuable intermediates for the synthesis of highly functionalized cyclic compounds. These compounds, whivh can be easily synthesized by diastereo-or enantio-selective addition of allylic organometallic reagents to (chiral) imines, can undergo different types of functionalization of the two C=C double bonds, for example epoxidation, dihydroxylation and transition metal catalyzed ring closure reactions such as metathesis reactions.

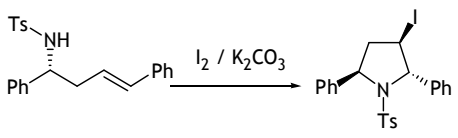
Alexakis synthesized the chiral *bis*-piperazine **24** starting from the diaminodiene **21** by preliminary hydroboration/oxidation step and subsequent ring closure through the di-tosylate intermediate [23].



Our research group has been very active in this field of research, for example we deswcribed the cycization of the diaminodiene **21** to 4,5-diaminodimethylcyclohexanes by reductive cyclozirconation, that proceed with good yield and fair stereoselectivity. Particularly, using preformed dibutylzirconocene Cp_2ZrBu_2 (4eq.), the 4(*R*),5(*S*)-diamino-4(*S*),5(*S*)-dimethylcyclohexane was the major stereoisomer, whereas using the Cp_2ZrCl_2 (10%)/BuMgCl (5 eq) system the preferential formation of the 1(*R*),2(*R*)-diamino-4(*S*),5(*S*)-dimethylcyclohexane was observed[24]. This reaction protocol was then extended to 3,6-disubstituted diamonodienes[25].



The reaction of aminoalkene moieties with electophiles, mainly halogens, mercury salts and selenium derivatives, has been widely exploited for the synthesis of azaheterocycles. Davies studied the iodine mediated cyclization of some substitutued homoallylic sulphonamides, which gave *trans*-2,5-disubstituted-iodopirrolidines as the major products. In this case the 5-*endo* cyclization is favored over the 4-*exo* as stated by the Baldwin's rules[26].



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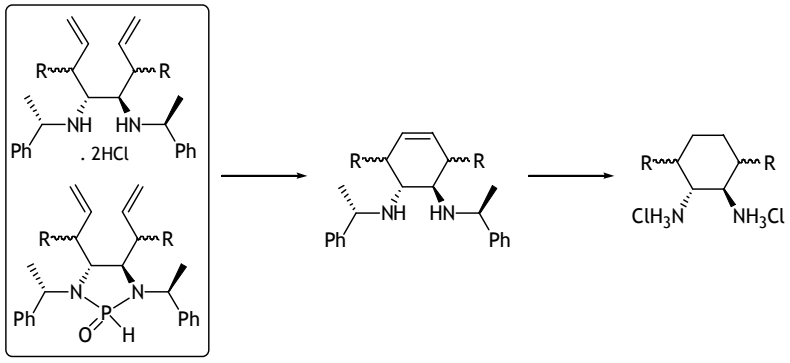
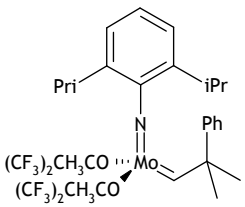
Chapter 2

Stereoselective Synthesis of 3,6-Disubstituted 1,2-Diaminocyclohexanes by Ring Closing Metathesis of 4,5-Diamino-1,7-octadiene derivatives

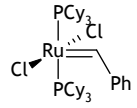


2.1 Introduction

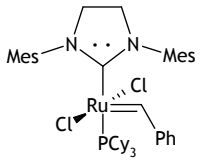
The ring closing metathesis (RCM) of 1,n-dienes has been widely applied for the construction of nitrogen containing compounds, for example natural alkaloids containing the pyrrolidine or piperidine ring[1] and amino-cycloalkenes.[2] A number of molybdenum- and especially ruthenium-carbene complexes are now available for the metathesis reaction.



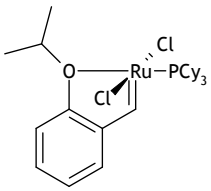
Schrock's catalyst
1



1st gen. Grubbs' catalyst
2



2nd gen. Grubbs' catalyst
3



Hoveyda's recyclable catalyst
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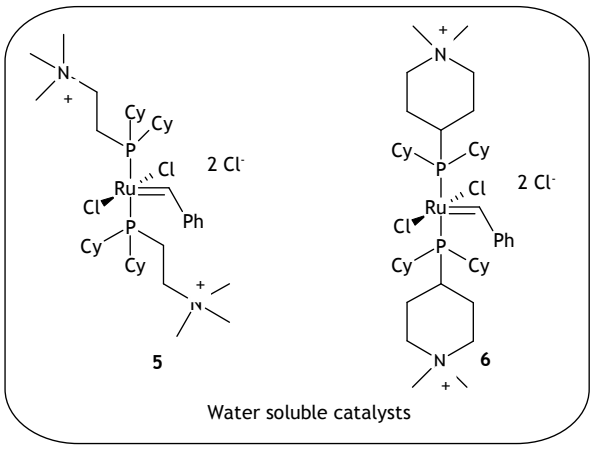
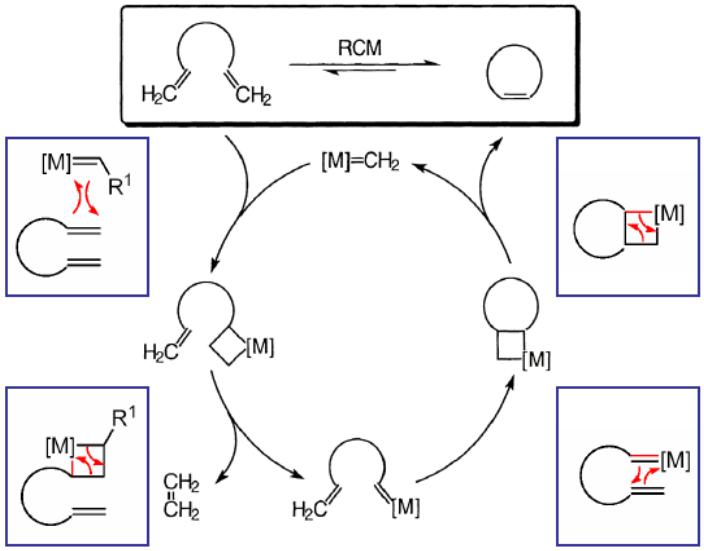


5 **6**

Water soluble catalysts

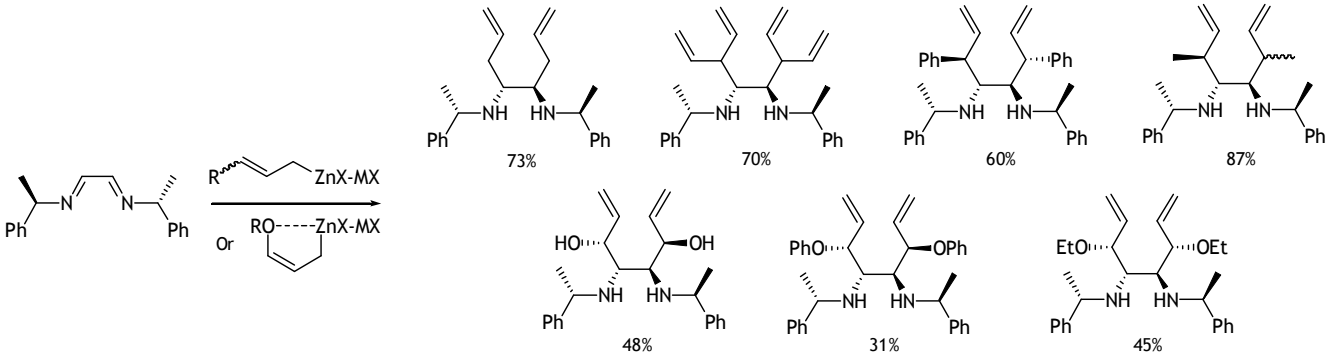
The Schrock's molybdenum-based catalyst **1**, was the first structurally defined catalyst, but despite its superior reactivity, especially for hindered olefins, its instability and low tolerance to many functional groups limited its use. The ruthenium-based Grubbs' catalyst **2** is stable to air and easier to handle, but less reactive, and has become the most popular reagent for the metathesis reaction. The increasing interest to the RCM reaction led to the development of a variety of new reagents, like the 2nd generation Grubbs' catalyst **3**, where the substitution of a phosphine ligand with an heterocyclic carbene increased both its termal stability and reactivity, particularly in the reaction of electron-poor olefins. Moreover, the reagent **4**, synthesized by Hoveyda, is stable enough to be recovered at the end of the reaction and reused several times. Also water-soluble compounds like **5** e **6** have been studied.

The mechanism of the RCM reaction has been studied in detail, but can be easily summarized by a series of [2+2] reversible cycloaddition steps between a metal-alkylidene complex and an alkene, leading to metallacyclobutanes[3]. The equilibria are shifted towards the formation of the cycloalkene, as ethylene is evolved, and the catalytically active species is regenerated. The RCM reaction is usually exploited for the construction of five- or six- membered rings but has been also successful employed for macrocyclization reactions.

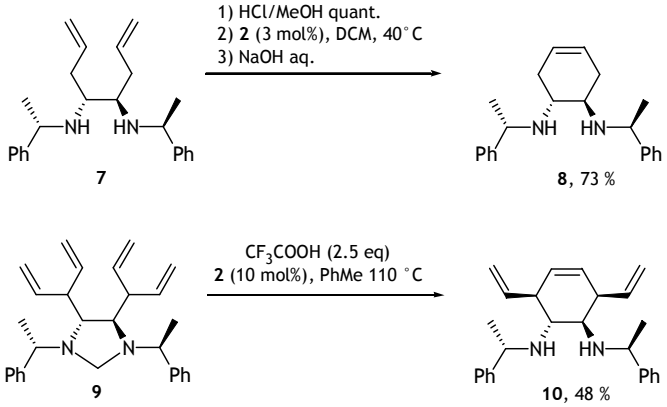


Configurationally pure 4,5-diamino-1,7-octadienes and 3,6-disubstituted-derivatives **c-e 1** are available by the double addition of γ-substituted allylzinc reagents to the optically pure 1,2-*bis*-imine derived from glyoxal and (*S*)-1-phenylethylamine.[4] In the reactions of γ-

substituted allylzinc compounds four stereocenters are newly created in the products **1**: the configuration of the α-amino stereocenters (C4,C5) is controlled by the chiral auxiliary, whereas the configuration of the stereocenters C3,C6 depends on the *E*/*Z* configuration of the C=C bond in the allylic zinc reagent.



It is known that both 1st and 2nd gen. Grubbs' catalysts are sensible to the amine moiety so a protection step is usually required. Our research group had previously reported[5] that the dihydrochloride of the (4*R*,5*R*)-4,5-diamino-1,7-octadiene derivative **7** can be converted to the *N*,*N*'-disubstituted-1,2-diaminocyclohex-4-ene **8** using the first generation Grubbs complex **2** as the catalyst.



On the other hand, the cyclization of the vinyl-substituted diaminodiene could be achieved with moderate diastereoselectivity through formation of the formaldehyde aminal **9**, which was then converted to the diaminocyclohexene **10** in the presence of trifluoroacetic acid in refluxing toluene. In these conditions, the hydrolysis of the imidazolidine ring was due, probably to the presence of traces of water in the solvent or reagents.[5b]

The interest in 1,2-diaminocyclohexenes stems from their potential as intermediates for the construction of more functionalized compounds, owing to the possible transformation

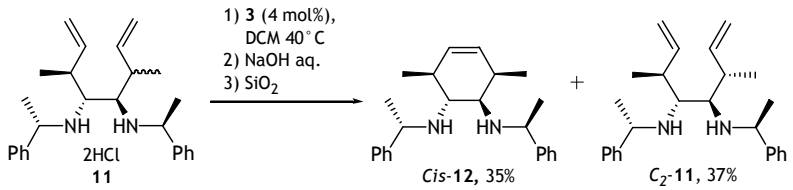
of the alkene function, for example epoxidation and dihydroxylation. Moreover, hydrogenation of the 3,6-disubsstituted derivatives provides access to saturated compounds which can act as novel chiral N,N-ligands of metal species. As a matter of fact, the effect of substituents on the activity and enatiooselectivity of salen complexes featuring a substituted cyclohexane ring has become an important field of investigation.[6] Moreover, polyhydroxylated diaminocyclohexenes (diaminoconduritols) and –cyclohexanes are potentially active as glycosidase inhibitors and can form cytostatic platinum complexes.[7]

Since it was apparent from the previous results that the RCM reaction of these class of compounds was strongly affected by the steric effects of the allylic substituents R, we continued the investigation on several 3,6-disubstituted compounds, aiming to find out suitable protocols for their cyclization.

2.2. RCM of substituted 4,5-diamino-1,7-octadienes dihydrochlorides

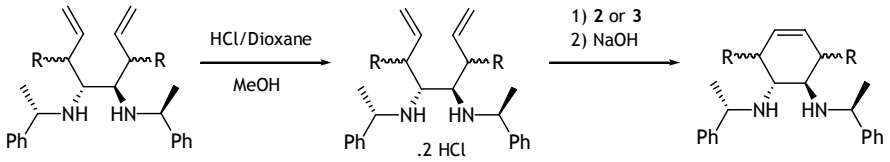
The dihydrochlorides of all diaminodienes were obtained in quantitative yields by reaction with anhydrous HCl in MeOH for 10 min, followed by removal of the solvent. All the results of the RCM reactions carried out on these salts are summarized in Table 1.

At first, we examined the RCM reaction of the dimethyl substituted diaminodiene **11** which was easily obtained as a 55:45 mixture of epimers by the addition of crotylzinc bromide to the glyoxal diimine, and were very difficultly separated by column chromatography. We observed that the ruthenium catalysts **2** and **3** displayed different activity in the reaction of **11-2HCl**. Working with catalyst **2** in refluxing CH_2Cl_2 no reaction was observed after 6 h. Instead, catalyst **3** (5 mol%) in the same conditions was able to discriminate at a high degree the two epimers: the C_1-symmetric diastereomer C_1-**11** was quickly consumed and converted to *cis*-**12**, while the C_2-symmetric isomer C_2-**11** did not react, as determined by GC/MS analysis of the reaction mixture. The diaminocyclohexene *cis*-**12** and unreacted C_2-**11** were separated by SiO_2 column chromatography and isolated with 35 and 37% yields, respectively. Hence, the preliminary separation of the two diastereomers of **11**, which is tedious and incomplete on a large scale, is unnecessary.



Applying the same reaction condition to the dihydroxy-substituted compound, we observed almost complete conversion using 7 mol% of catalyst **3**, and obtained the desired diamino-diol with good yield (70%) after purification. Even in this case, the 1st generation Grubbs' catalyst **2** was ineffective. With this regard, it should be underlined that previously described syntheses of oxygen-substituted cyclohexenes by RCM reactions were generally achieved through protection of the hydroxy functions in the starting 1,7-dienes, and required high loadings of the catalyst **2** (up to 30 mol%), high temperatures and long reaction times.[8] Moreover, the isomerization of the allylic secondary alcohol moiety to ethyl ketone was a competitive side reaction.[8c, 9]

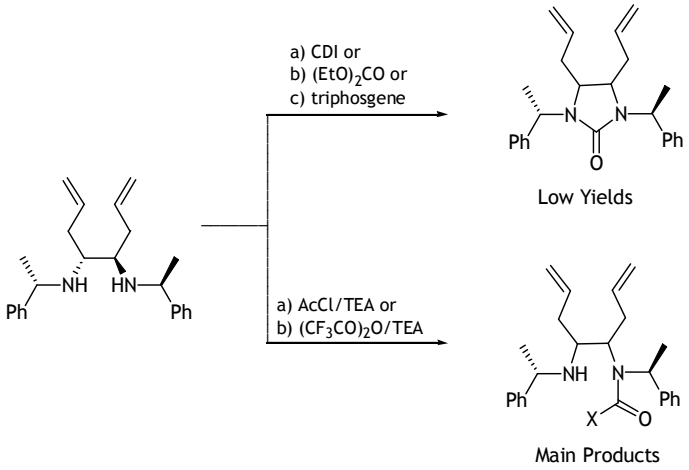
Unluckily, this reaction protocol proved to be unsuccessful with the ethoxy- and phenoxy-substituted substrates and no improvement was observed raising the reaction temperature or using higher catalyst loadings. In all cases, we recovered the starting material unchanged , with no detectable contamination by cross-metathesis products. This led us to think that bulky R substituents prevent the formation of the metallacyclobutane in the first step of the catalytic cycle. It should be also pointed out that the 1st generation Grubbs' catalyst was again ineffective.



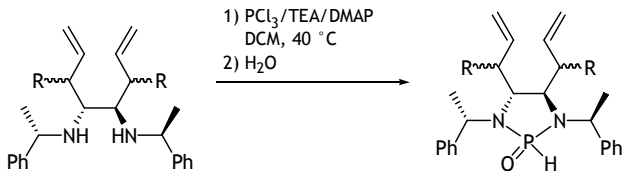
R	Solvent	Temp (°C)	Cat %	Time (h)	Yield %
OH	CH_2Cl_2	40	**3**, 7	4	70
OH	CH_2Cl_2	40	**2**, 5	3	No reaction
Me (55:45 mixture)	CH_2Cl_2	40	**3**, 5	6	35 (C_1)
Me (55:45 mixture)	CH_2Cl_2	40	**2**, 4	6	No reaction
OEt (75:25 mixture)	CH_2Cl_2	40	**3**, 7	4	No reaction
OPh	CH_2Cl_2	40	**3**, 10	6	No reaction
OPh	toluene	110	**3**, 10	3	No reaction

2.2 RCM of 3,6-disubstituted 4,5-diamino-1,7-octadienes through formation of their phosphorous acid diamides.

We have made some attempts to protect the amine moieties to avoid the acidic conditions that can degrade the catalyst in the methatesis reaction, but with poor success. Reaction of **7** with carbonic acid derivatives like 1,1'-carbonyldiimidazole (Staab reagent), triphosgene or diethyl carbonate yielded cyclic ureas in low yields. On the other hand with acetyl chloride and trifluoroacetic anhydride the monoamide was the main product.



Then we found that the diamine moiety could be easily protected as a cyclic phosphorous diamide by reaction with PCl_3 then quenching with water. In addition, this protection can be simply removed by hydrolysis with a methanolic solution of HCl[10]. It should be noted that the quaternary phosphorous atom in a C_1-symmetric diamide like **15** is a new stereocenter. In these case, a 1:1 mixture of epimers was observed by ^1H-, ^{13}C- and ^{31}P-NMR analyses.



R	Yield %	
Me (trans)	93	"C_2"-**13**
Me (55:45 mixture)	87	**13**
Vinyl	92	**14**

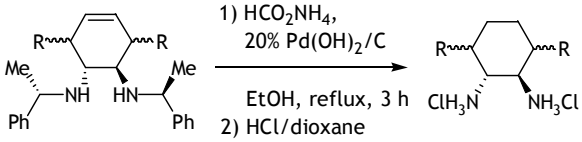
OEt (75:25 mixture)	75	**15**
Ph	94	**16**
OPh	100	**17**

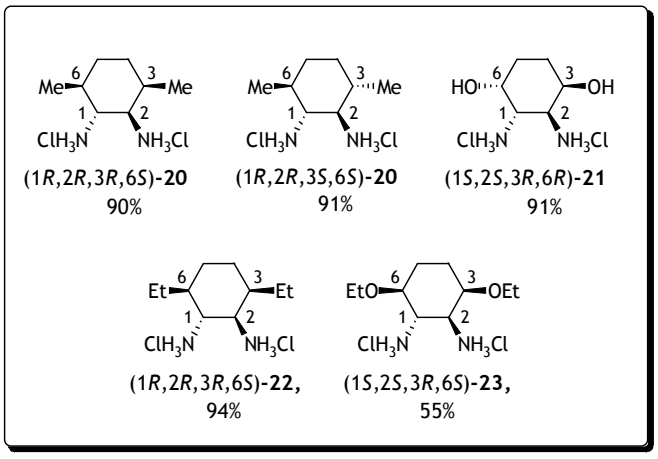
The products were used in the RCM step without further purification, then the protection was immediately removed, because the free diamines were more easily purified by column chromatography. With the phosphorous diamide **13** we observed a quick cyclization in the presence of 4 mol% of catalyst **3** in CH_2Cl_2 at 40 °C. After acidic hydrolysis of the reaction mixture, the desired free diamine **18** was isolated with 92% yield. The *trans*-dimethyl-substituted diastereomer "C_2"-**18** was similarly prepared with good yield starting from "C_2"-**11**, which had been recovered from the previously described reaction. The phosphorous diamide **14** with pentadienyl-substituents was similarly prepared but we observed that it did not undergo cyclization in the presence of catalyst **2**, but the ring closure was moderately successful in the presence of the catalyst **3** (7 mol%) in refluxing benzene for 3 h. Better reaction conditions were found using CH_2Cl_2 as the solvent at 40 °C. By this way, *cis*-**19** was isolated with 53% yield after chromatographic separation from minor amounts of the *trans*-diastereomer and unreacted **14**.

Either the dihydrochloride and the phosphorous diamide **15** of the diethoxy substituted substrate (75:25 mixture of diastereomers, the prevalent one had C_1-symmetry) were submitted to RCM reactions in refluxing CH_2Cl_2 (entries 11, 12) but only the latter could be converted with moderate yield to the desired cyclohexene *cis*-**20**. Unfortunately, the phosphorous diamides **16** prepared from phenyl-substituted and the phenoxy-substituted **17** diaminodienes did not undergo cyclization either in CH_2Cl_2 and in benzene or toluene at the reflux temperature even using 10 mmol% of catalyst **6.** From these results, it is clear that the RCM reaction of 3,6-disubstituted-4,5-diamino-1,7-octadienes was best accomplished through the cyclic phosphorous diamides by using the ruthenium catalyst **3** in CH_2Cl_2 at 40 °C. The reaction was very sensitive to steric effects, being affected by the nature of the substituents and the configuration of the inherent stereocenters. Particularly, cyclohexenes were more easily formed when the allylic substituents could assume the relative *cis*-relationship in the six-membered ring.

R	Solvent	Temp (°C)	Cat %	Time (h)	Yield %
Me (trans)	DCM	40	**3**, 4	3	"C_2"-**12**, 74
Me (55:45 mixture)	DCM	40	**3**, 4	3	**12**, 92
Vinyl	DCM	40	**3**, 7	3	*cis*-**18**, 53
Vinyl	PhMe	110	**2**, 7	6	No reaction
OEt (75:25 mixture)	DCM	40	**3**, 5	3	*cis*-**19**,38
Ph	DCM	40	**3**, 10	6	No reaction
Ph	C_6H_6	80	**2**, 10	6	No reaction
OPh	DCM	40	**3**, 10	6	No reaction
OPh	PhMe	110	**3**, 10	4	No reaction

Finally, the *N*-unsubstituted diaminocyclohexanes (1*R*,2*R*,3*R*,6*S*)-**20**, (1*R*,2*R*,3*S*,6*S*)-**20**, (1*S*,2*S*,3*R*,6*R*)-**21,** (1*R*,2*R*,3*R*,6*S*)-**22** and (1*S*,2*S*,3*R*,6*S*)-**23** were prepared from **12-19** by palladium-catalyzed hydrogenation/hydrogenolysis in refluxing ethanol. Particularly, the diethyl-substituted compound **22** was obtained from the vinyl-substituted precursor *cis*-**18**.





It should be observed that the RCM reactions allowed us to prepare new 1,2-diaminocyclohexane derivatives, where both the amino groups are equatorially oriented and the C3,C6 substituents are in one of the three possible relative orientations: axial-equatorial (**21-23**), equatorial-equatorial (**21**) and axial-axial (**22**). The effect of the

relative stereochemistry of the C3/C6 substituents, and their size should now be assessed in a number of asymmetric reactions, like those catalyzed by salen complexes.

Experimental Section

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent in N_2 atmosphere before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), CH_2Cl_2 (P_2O_5). Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR spectra were recorded on a Varian Gemini instrument at 300 or 200 MHz for samples in $CDCl_3$ which was stored over Mg: ^1H chemical shifts are reported in ppm relative to $CHCl_3$ δ_H 7.27, δ_C 77.0) and *J*-values are given in Hz. ^{31}P NMR spectra were recorded on a Varian Mercury 400 spectrometer at 161.90 MHz; chemical shifts are referenced to external standard 85% H_3PO_4. MS spectra were taken at an ionizing voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. The ruthenium catalysts **5** and **6** were purchased from Aldrich. The metathesis reactions were carried in a flame-dried apparatus under a static atmosphere of dry Ar.

General procedure for the RCM reactions of diaminodienes 1 through their dihydrochlorides

To the stirred solution of diaminodiene (2 mmol) in MeOH (5 mL) was added HCl (4 M in dioxane, 1 mL), then the solvent was removed at reduced pressure to leave an off-white solid. This is dissolved in CH_2Cl_2 (6 mL), the complex **3** (5-7 mol%) was added while Ar was bubbled through the solution (0.5 min), and the solution was stirred at 40 °C until (almost) complete conversion (TLC analysis). The cooled reaction mixture was treated with 2 M NaOH (5 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 5 mL). The collected organic layers were dried over $CaCl_2$ and concentrated at reduced pressure to leave a greyish solid. Pure diaminocyclohexenes were obtained by column chromatography (SiO_2, cyclohexane/ethyl acetate mixtures).

(1*R*,2*R*,3*R*,6*S*)-3,6-dimethyl-*N*,*N*'-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*cis*-12)

This compound was obtained as an oil starting from the (6*R*,6*S*)-mixture of **11**-2HCl through chromatographic separation of unreacted (C_2)-**11**.

$[\alpha]_D^{25}$ –61.5 (c 0.22, $CHCl_3$).

IR (neat): 3340, 3295, 3062, 3023, 1602, 1370 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 and 1.11 (6 H, 2 d, *J* = 6.9 Hz), 1.22 and 1.48 (6 H, 2 d, *J* = 6.6 Hz), 1.27 (1 H, s) 2.0 (2 H, m), 2.07 (1 H, dd, *J* = 9.9, 8.7 Hz), 2.36 (1 H, dd, *J* = 15.3, 5.1 Hz), 2.40 (1 H, m), 3.68 and 3.81 (2 H, 2 q, *J* = 6.6 Hz), 5.21 (1 H, ddd, *J* = 9.9, 1.8, 1.5 Hz), 5.46 (1 H, ddd, *J* = 9.9, 4.8, 2.4 Hz), 7.1-7.4 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 20.2, 24.1, 25.6, 31.1, 41.0, 53.5, 55.7, 56.7, 58.4, 126.7, 127.2, 128.1, 128.3, 130.3, 131.5. GC/MS *m*/*z* (relative intensity): 105 (100), 214 (65), 110 (51), 120 (17), 348 (2, M^+).

Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.46; H, 9.29; N, 8.07.

(1*R*,4*R*,5*S*,6*S*)-5,6-bis{[(1*S*)-1-phenylethyl]amino}cyclohex-2-ene-1,4-diol.

White powder: mp 120-122 °C.

$[\alpha]_D^{25}$ –11.4 (c 0.63, $CHCl_3$).

IR (KBr): 3318, 3027, 1600, 1324, 1259 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (6 H, d, *J* = 6.6 Hz), 1.9-2.9 (4 H, broad), 2.45 (2 H, m), 3.81 (2 H, q, *J* = 6.6 Hz), 4.06 (2 H, m), 5.97 (2 H, dd, *J* = 1.4, 2.8), 7.2-7.4 (10 H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 52.5, 55.1, 62.3, 126.6, 127.2, 128.6, 130.5, 145.1.

Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.67; H, 8.04; N, 7.92.

Preparation of the phosphorous diamides.

To the stirred solution of the diaminodiene (2 mmol) in DCM (10 mL) was added Et_3N (2.02 g, 20 mmol), DMAP (10 mg). Freshly distilled PCl_3 (0.55 g, 4 mmol) was added at 0 °C and the mixture was stirred for 3 h at reflux temperature. After cooling at 0 °C, H_2O (10 mL) was slowly added (**care!**), CH_2Cl_2 was removed at reduced pressure, and the organic materials were extracted with Et_2O (3 × 10 mL). The ethereal layers were collected, then Na_2SO_4 and SiO_2 (1 g) were added, the mixture was stirred for 30 min, then filtered through a small pad of Celite, and the organic solution was concentrated at reduced pressure. The products were used avoiding further purification.

(4*R*,5*R*)-1,3-bis[(1*S*)-1-phenylethyl]-4,5-bis(1-vinylprop-2-en-1-yl)-1,3,2-diazaphospholidine 2-oxide (14)

Whitish oil.

$[\alpha]_D^{25}$ +21.6 (c 0.44, $CHCl_3$).

IR (neat): 3428, 3077, 2360 (P-H), 1635, 1226 (P=O), 1129, 1037, 998, 918, 773, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 7.3 Hz, 3 H), 1.78 (d, *J* = 7.3 Hz, 3 H), 2.55-2.75 (m, 3 H), 2.85-2.95 (m, 1 H), 4.10-4.20 (m, 1 H), 4.25-4.55 (m, 3 H), 4.75-5.25 (m, 7 H), 5.30-5.50 (m, 1 H), 5.50-5.70 (m, 2 H), 7.25-7.45 (m, 8 H), 7.55-7.65 (m, 2 H), 8.04 (d, $^1J_{P,H}$ = 609 Hz, 1 H, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.42 (d, $^3J_{C,P}$ = 3.6 Hz, CH_3), 21.4 (d, $^3J_{C,P}$ = 3.6 Hz, CH_3), 51.2 (*C*HCH=CH_2), 51.6 (*C*HCH=CH_2), 55.85 (d, $^2J_{C,P}$ = 7.2 Hz, *C*HCH_3), 56.2 (d, $^2J_{C,P}$ = 6.1 Hz, *C*HCH_3), 59.7 (d, $^2J_{C,P}$ = 9.0 Hz, CH*C*HN), 62.6 (d, $^2J_{C,P}$ = 7.8 Hz, CH*C*HN), 116.6 (CH_2=), 116.9 (CH_2=), 117.6 (CH_2=), 117.8 (CH_2=), 127.4, 127.5, 127.85, 128.0, 128.35, 128.6 (6 lines for arom. CH), 136.1 (CH=), 136.2 (CH=), 136.9 (CH=), 137.25 (CH=), 142.8 (arom.), 143.1 (C arom.).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 8.9 (dm, $^1J_{P,H}$ = 609 Hz).

(4*R*,5*R*)-4,5-bis[(1*S*)-1-methylprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine-2-oxide (C_2-13)

Whitish oil.

$[\alpha]_D^{25}$ −31.2 (c 0.73, $CHCl_3$).

IR (neat): 3445, 3065, 3035, 2346 (P-H), 1638, 1600, 1228 (P=O), 1130, 1033, 913, 802, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 7.1 Hz, 3 H), 0.79 (d, *J* = 7.1 Hz, 3 H), 1.76 (d, *J* = 7.0 Hz, 3 H), 1.82 (d, *J* = 7.0 Hz, 3 H), 2.20-2.49 (m, 2 H), 2.58-2.90 (m, 2 H), 4.12-4.42 (m, 2 H), 4.52-5.04 (m, 4 H), 5.15-5.34 (m, 1 H), 5.65-5.84 (m, 1 H), 7.23-7.43 (m, 8 H), 7.52-7.60 (m, 2 H), 7.96 (d, $^1J_{P,H}$ = 609 Hz, 1 H, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (*C*H_3CHCH=), 15.6 (*C*H_3CHCH=), 21.6 (d, $^3J_{C,P}$ = 4.7 Hz, *C*H_3CHN), 21.7 (d, $^3J_{C,P}$ = 5.2 Hz, *C*H_3CHN), 38.2 (*C*HCH=CH_2), 38.7 (*C*HCH=CH_2), 55.0 (d, $^2J_{C,P}$ = 6.9 Hz, N*C*HCH_3), 55.1 (d, $^2J_{C,P}$ = 7.6 Hz, N*C*HCH_3), 60.1 (d, $^2J_{C,P}$ = 9.1 Hz, CH*C*HN), 62.55 (d, $^2J_{C,P}$ = 8.2 Hz, CH*C*HN), 115.5 (CH_2=), 116.0 (CH_2=), 127.3, 127.4, 127.7, 127.9, 128.2, 128.4 (6 lines for arom. CH), 138.3 (CH=), 139.3, (CH=), 142.35 (arom.), 142.8 (arom.).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 9.9 (dm, $^1J_{P,H}$ = 609 Hz).

(4*R*,5*R*)-1,3-bis[(1*S*)-1-phenylethyl]-4,5-bis[(1*R*)-1-phenylprop-2-en-1-yl]-1,3,2-diazaphospholidine 2-oxide (16)

White solid: m.p. 210-215 °C (dec).

$[\alpha]_D^{25}$ +19.2 (c 0.39, $CHCl_3$).

IR (KBr): 3429, 3026, 2329 (P-H), 1600, 1226 (P=O), 1128, 1035, 988, 933, 900, 770, 701, 635, 542 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 7.2 Hz, 3 H), 1.44 (d, *J* = 7.2 Hz, 3 H), 2.58-3.05 (m, 5 H), 3.05-3.20 (m, 1 H), 3.80 (d, *J* = 17.3 Hz, 1 H), 3.95 (d, *J* = 17.3 Hz, 1 H), 4.69 (dd, *J* = 10.4 Hz, *J* = 1.8 Hz, 1 H), 4.77 (dd, *J* = 10.4 Hz, *J* = 1.8 Hz, 1 H), 5.50-5.70 (m, 2 H), 7.05-7.20 (m, 4 H), 7.20-7.45 (m, 14 H), 7.50-7.62 (m, 2 H), 8.30 (d, $^1J_{P,H}$ = 602 Hz, 1 H, PH),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (d, $^3J_{C,P}$ = 6.0 Hz, CH_3), 21.3 (d, $^3J_{C,P}$ = 5.0 Hz, CH_3), 53.8 (*C*HCH=CH_2), 54.8 (*C*HCH=CH_2), 56.0 (d, $^2J_{C,P}$ = 6.8 Hz, *C*HCH_3), 57.0 (d, $^2J_{C,P}$ = 5.0 Hz, *C*HCH_3), 61.9 (d, $^2J_{C,P}$ = 9.7 Hz, CH*C*HN), 65.6 (d, $^2J_{C,P}$ = 7.7 Hz, CH*C*HN), 117.6 (CH_2=), 117.9 (CH_2=), 126.75, 126.92, 127.2, 127.4, 127.7, 128.1, 128.35, 128.4, 128.4, 128.6 (10 lines, 2 sign. overl. for arom. CH), 137.2 (CH=), 137.7 (CH=), 141.4 (arom.), 141.7 (C arom.), 143.9 (arom.), 143.95 (arom.).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 7.2 (dm, $^1J_{P,H}$ = 602 Hz).

(4*S*,5*S*)-4-[(1*R*,*S*1-ethoxyprop-2-en-1-yl]-5-[(1*S*)-1-ethoxyprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-oxide and (4*S*,5*S*)-4,5-bis[(1*S*)-1-ethoxyprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-oxide (15, dr 70:30)

Yellowish oil.

$[\alpha]_D^{25}$ –7.0 (c 0.68, $CHCl_3$).

IR (neat): 3433, 3062, 3028, 2346 (P-H), 1640, 1226 (P=O), 1131, 929, 772, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.0 Hz, 3 H), 1.01 (t, *J* = 7.0 Hz, 3 H), 1.07 (t, *J* = 7.0 Hz, 3 H), 1.11 (t, *J* = 7.0 Hz, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H), 1.69 (d, *J* = 7.3 Hz, 3 H) 1.70 (d, *J* = 7.0 Hz, 3 H), 1.71 (d, *J* = 7.1 Hz, 3 H), 1.72 (d, *J* = 7.2 Hz, 3 H), 1.76 (d, *J* = 7.0 Hz, 3 H), 1.78 (d, *J* = 6.5 Hz, 3 H), 2.40-3.60 (m, 24 H), 4.10-5.90 (m, 24 H), 7.20-7.50 (m, 24 H), 7.50-7.65 (m, 6 H), 7.96 (d, $^1J_{P,H}$ = 609 Hz, 2 H, PH), 8.07 (d, $^1J_{P,H}$ = 604 Hz, 1 H, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9 (*C*H_3CH_2OCH=), 15.0 (*C*H_3CH_2OCH=), 15.1 (*C*H_3CH_2OCH=), 15.2 (*C*H_3CH_2OCH=), 15.2 (*C*H_3CH_2OCH=), 15.3 (*C*H_3CH_2OCH=), 21.2 (d, $^3J_{C,P}$ = 3.4 Hz, CH_3), 21.2 (d, $^3J_{C,P}$ = 3.2 Hz, CH_3), 21.3 (d, $^3J_{C,P}$ = 4.3 Hz, CH_3), 21.4 (d, $^3J_{C,P}$ = 3.7 Hz, CH_3), 21.5

(d, $^{3}J_{C,P}$ = 5.5 Hz, CH_3), 21.7 (d, $^{3}J_{C,P}$ = 4.9 Hz, CH_3), 55.2 (d, $^{2}J_{C,P}$ = 6.0 Hz, *C*HCH$_3$), 55.6 (d, $^{2}J_{C,P}$ = 7.1 Hz, *C*HCH$_3$), 55.8 (d, $^{2}J_{C,P}$ = 7.5 Hz, *C*HCH$_3$), 55.9 (d, $^{2}J_{C,P}$ = 6.1 Hz, *C*HCH$_3$), 56.25 (d, $^{2}J_{C,P}$ = 7.0 Hz, *C*HCH$_3$), 56.9 (d, $^{2}J_{C,P}$ = 5.7 Hz, *C*HCH$_3$), 57.3 (d, $^{2}J_{C,P}$ = 8.7 Hz, CH*C*HN), 56.2 (d, $^{2}J_{C,P}$ = 9.6 Hz, CH*C*HN), 58.8 (d, $^{2}J_{C,P}$ = 9.6 Hz, CH*C*HN), 60.8 (d, $^{2}J_{C,P}$ = 8.2 Hz, CH*C*HN), 61.35 (d, $^{2}J_{C,P}$ = 7.8 Hz, CH*C*HN), 61.6 (d, $^{2}J_{C,P}$ = 8.4 Hz, CH*C*HN), 63.95 (OCH_2), 64.0 (OCH_2), 64.15 (OCH_2), 64.3 (OCH_2), 64.5 (OCH_2), 64.5 (OCH_2), 81.1 (*C*HCH=CH_2), 81.6 (*C*HCH=CH_2), 82.7 (*C*HCH=CH_2), 82.9 (*C*HCH=CH_2), 83.2 (*C*HCH=CH_2), 83.5 (*C*HCH=CH_2), 117.9 (CH_2=), 118.0 (CH_2=), 118.9 (CH_2= 3 sign. overl.), 119.7 (CH_2=), 127.15, 127.2, 127.27, 127.3, 127.3, 127.4, 127.5, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.2, 128.2, 128.3, 128.23 128.5 (18 lines for arom. CH), 134.6 (CH=), 135.0 (CH=), 135.1 (CH=), 135.38 (CH=), 135.58 (CH=), 135.69 (CH=), 143.10 (arom.), 143.35 (arom.), 143.4 (arom.), 143.4 (arom.), 143.55 (arom.), 143.8 (arom.).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 12.1 (dm, $^{1}J_{P,H}$ = 609 Hz), ¤ = 11.1 (dm, $^{1}J_{P,H}$ = 609 Hz), and ¤ = 8.3 (dm, $^{1}J_{P,H}$ = 604 Hz).

(4*S*,5*S*)-4,5-bis[(1*S*)-1-phenoxyprop-2-en-1-yl]-1,3-bis[(1*S*)-1-phenylethyl]-1,3,2-diazaphospholidine 2-oxide (17)

White solid: m.p. 125-134 (dec.).

$[\alpha]_D^{25}$ +1.7 (c 1.8, $CHCl_3$).

IR (KBr): 3406, 3070, 3042, 2365 (PH), 1646, 1597, 1228 (P=O), 1118, 1031, 928, 803, 753, 700, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 7.0 Hz, 3 H), 1.79 (d, *J* = 7.0 Hz, 3 H), 3.28-3.41 (m, 1 H), 3.41-3.55 (m,. 1 H), 4.16-4.34 (m, 2 H), 4.38-4.60 (m, 2 H), 4.98-5.30 (m, 4 H), 5.40-5.57 (m, 1 H), 5.60-5.78 (m, 1 H), 6.65 (d, *J* = 8.1 Hz, 2 H), 6.74 (d, *J* = 8.1 Hz, 2 H), 6.88-7.00 (m, 2 H), 7.10-7.30 (m, 10 H), 7.34-7.53 (m, 4 H), 8.06 (d, $^{1}J_{P,H}$ = 613 Hz, 1 H, PH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.83 (d, $^{3}J_{C,P}$ = 4.2 Hz, CH_3), 21.3 (d, $^{3}J_{C,P}$ = 4.2 Hz, CH_3), 54.6 (d, $^{2}J_{C,P}$ = 6.5 Hz, *C*HCH$_3$), 55.0 (d, $^{2}J_{C,P}$ = 8.0 Hz, *C*HCH$_3$), 57.7 (d, $^{2}J_{C,P}$ = 8.9 Hz, CH*C*HN), 60.14 (d, $^{2}J_{C,P}$ = 8.1 Hz, CH*C*HN), 78.4 (*C*HCH=CH_2), 79.4 (*C*HCH=CH_2), 115.7 (arom. CH), 116.3 (arom. CH), 118.6 (CH_2=), 119.0 (CH_2=), 121.10, 121.15, 127.3, 127.4, 127.5, 127.5, 128.4, 128.5, 129.2, 129.3 (10 lines for arom. CH), 133.65 (CH=), 134.5 (CH=), 142.35 (arom.), 142.4 (arom.), 142.7 (arom.), 142.7 (arom.).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 13.4 (dm, $^{1}J_{P,H}$ = 613 Hz).

General procedure for the RCM reactions of phosphorous acid diamides.

The complex **3** (43 mg, 0.05 mmol) was added to the stirred solution of the phosphorous diamide (2 mmol) in CH_2Cl_2 (6 mL) while Ar was bubbled through the solution (0.5 min), and the solution was stirred at 40 °C. An equal amount of complex **3** was added after 1.5 h and the mixture was further stirred at 40 °C for 1.5-2 h. Solvent was removed at reduced pressure and the residue was dissolved in MeOH (8 mL, then HCl (4 M in dioxane, 2 mL) was added and the mixture was stirred overnight. The solvent was removed at reduced pressure and the residue was treated with Et_2O (10 mL), H_2O (10 mL) and solid NaOH until pH 11. The organic phase was separated and the aqueous layer was further extracted with Et_2O (3 × 5 mL). The collected organic layers were dried over Na_2SO_4 and concentrated at reduced pressure to leave a yellowish oil. The pure diaminocyclohexene was obtained by column chromatography (SiO_2, cyclohexane/ethyl acetate mixtures).

Compound ***Cis*-18** was previously described.[3b]

(1*R*,2*R*,3*S*,6*S*)-3,6-dimethyl-*N*,*N*'-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*trans*-12)

Yellowish oil; $[\alpha]_D^{25}$ +64.2 (c 1.74, $CHCl_3$).

IR (neat): 3317, 3082, 3060, 3011, 1602, 1368 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (6 H, d, *J* = 5.7 Hz), 1.28 (6 H, d, *J* = 6.6 Hz), 1.68 (2 H, broad m), 2.04 (4 H, m), 3.89 (2 H, q, *J* = 6.6 Hz), 5.21 (2 H, s), 7.1-7.4 (10 H, m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 24.8, 40.6, 58.1, 62.3, 126.8, 127.1, 128.3, 131.4, 145.8.

GC/MS *m*/*z* (relative intensity): 105 (100), 214 (63), 110 (50), 120 (17), 348 (3, M^+).

Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.41; H, 9.29; N, 8.01.

(1*S*,2*S*,3*R*,6*S*)-3,6-diethoxy-*N*,*N*'-bis[(1*S*)-1-phenylethyl]cyclohex-4-ene-1,2-diamine (*Cis*-19)

Yellowish oil; $[\alpha]_D^{25}$ –82.7 (c 0.7, $CHCl_3$).

IR (neat): 3301, 3027, 1602, 1369, 1326, 1270, 1088 $\tilde{cm}^{-1}$.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 and 1.26 (6 H, 2 t, *J* = 7.0 Hz), 1.32 and 1.44 (6 H, 2 d, *J* = 6.2 Hz), 2.24 (2 H, dd, *J* = 11.4, 3.2 Hz), 2.55 (2 H, dd, *J* = 11.4, 8.0 Hz), 3.43 (1 H, dq, *J* = 1.8, 8.0), 3.5-3.75 (4 H, m), 3.75-3.95 (2 H, m), 4.17 (1 H, q, *J* = 6.6 Hz), 5.79 (1H, dd, *J* =1.8, 10.4 Hz), 5.90 (1H, ddd, *J* =1.2, 4.8, 10.4 Hz), 7.1-7.5 (10 H, m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.55, 15.8, 24.9, 25.8, 26.9, 54.0, 54.2, 55.4, 57.1, 64.1, 64.2, 68.5, 125.8, 126.3, 126.9, 127.0,127.0, 128.1, 128.5, 131.6, 145.3, 146.5.
GC/MS *m*/*z* (relative intensity): 105 (100), 57 (33), 77 (22), 161 (20), 106 (12), 266 (10), 120 (6).
Anal. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76,74; H, 8.91; N, 6.84.

General procedure for the preparation of 1,2-diaminocyclohexanes dihydrochlorides.
The mixture of 1,2-diaminocyclohexene **2** (1 mmol), HCO_2NH_4 (0.800 g, 12.5 mmol), 20% $Pd(OH)_2$/C (0.100 g) in EtOH (10 mL) was heated at reflux temperature for 3 h. The cooled mixture was filtered over a small pad of celite and the organic solution was treated with HCl (4 M in dioxane, 0.5 mL). Solvents were removed at reduced pressure to leave the diamine dihydrochloride as a white solid, >95% pure by 1H NMR.

(1*R*,2*R*,3*R*,6*S*)-3,6-dimethylcyclohexane-1,2-diaminium dichloride (*cis*-20)
M.p.: 200-210 °C (dec.).
$[\alpha]_D^{25}$ −8.4 (c 0.5, MeOH).
IR (KBr): 3420, 2500-3500 (broad), 1594, 1566, 1498 cm^{-1}.
^{1}H NMR (300 MHz, CD_3OD): δ = 1.13 (3 H, d, *J* = 7.2 Hz), 1.20 (3 H, d, *J* = 6.6 Hz), 1.50 (1 H, dt, *J* = 2.7, 12.9 Hz), 1.60-1.90 (4 H, m), 2,50 (1 H, m), 3.39 (1 H, dd, *J* = 10.5, 11.1 Hz), 3.66 (1 H, dd, *J* = 4.8, 10.5 Hz).
^{13}C NMR (75 MHz, CD_3OD): δ = 12.9, 18.8, 28.3, 30.9, 33.1, 37.3, 56.2, 56.4.
Anal. Calcd for $C_8H_{20}Cl_2N_2$: C, 44.66; H, 9.37; N, 13.02. Found: C, 44.47; H, 9.40; N, 12.97.

(1*R*,2*R*,3*S*,6*S*)-3,6-dimethylcyclohexane-1,2-diaminium dichloride (*trans*-20)
M.p.: 230-240 °C (dec.).
$[\alpha]_D^{25}$ +7.2 (c 1.3, MeOH).
IR (KBr): 3425, 2500-3400 (broad), 1594, 1520 $\tilde{cm}^{-1}$.
^{1}H NMR (300 MHz, CD_3OD): δ = 1.18 (6 H, d, *J* = 6.0 Hz), 1.34 (2 H, m), 1.82 (4 H, d, *J* = 7.5 Hz), 3.2 (2 H, d, *J* = 7.8 Hz).
^{13}C NMR (75 MHz, CD_3OD): δ = 19.0, 33.4, 37.1, 59.8.
Anal. Calcd for $C_8H_{20}Cl_2N_2$: C, 44.66; H, 9.37; N, 13.02. Found: C, 44.48; H, 9.41; N, 12.98.

(1*S*,2*S*,3*R*,6*R*)-3,6-dihydroxycyclohexane-1,2-diaminium dichloride (21)
M.p.: 200-210 °C (dec.).

$[\alpha]_D^{25}$ - 73.2 (c 0.17, MeOH).

IR (KBr): 3364, 2600-3200 (broad), 1549, 1205 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.60 (2 H, dd, *J* = 9.8, 4.2 Hz),1.89 (2 H, dd, *J* = 9.8, 1.2 Hz), 3.53 (2 H, m), 4.07 (2 H, m).

^{13}C NMR (75 MHz, CD_3OD): δ = 26.2, 53.3, 67.1.

Anal. Calcd for $C_6H_{16}Cl_2N_2O_2$: C, 32.89; H, 7.36; N, 12.79. Found: C, 32.75; H, 7.39; N, 12.75.

(1*S*,2*S*,3*R*,6*S*)-3,6-diethoxycyclohexane-1,2-diaminium dichloride (22)

The crude compound was isolated as a yellowish solid with 87% yield, then was washed with 8:1 Et_2O/MeOH mixture to leave a white solid with 55% yield.

M.p.: 175-185 °C (dec.).

$[\alpha]_D^{25}$ –14.1 (c 0.27, MeOH).

IR (KBr): 3413, 3143, 2200-2500 (broad), 1626, 1107 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.27 and 1.29 (6 H, 2 t, *J* = 6.9 Hz), 1.55 (2 H, m), 2.12 (1 H, m), 2.25 (1 H, m), 3.40-3.65 (4 H, m), 3.65-3.90 (3 H, m), 3.93 (1 H, s).

^{13}C NMR (50 MHz, CD_3OD): δ = 15.85, 15.9, 23.7, 24.1, 54.7, 55.5, 65.6, 66.0, 74.4, 77.7.

Anal. Calcd for $C_{10}H_{24}Cl_2N_2O_2$: C, 43.64; H, 8.79; N, 10.00. Found: C, 43 51; H, 8.82; N, 10.15.

(1*R*,2*R*,3*R*,6*S*)-3,6-diethylcyclohexane-1,2-diaminium dichloride (23)

M.p.: 170-180 °C (dec.).

$[\alpha]_D^{25}$ –3.8 (c 0.44, MeOH).

IR (KBr): 3436, 2500-3400 (broad), 1594, 1503 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 0.88 (6 H, t, *J* = 7.0 Hz), 1.1-1.7 (8 H, m), 1.7-1.8 (1 H, m), 1.9-2.1 (1 H, m), 3.26 (1 H, dd, *J* = 9.6, 8.0 Hz), 3.49 (1 H, dd, *J* = 9.6, 4.8).

^{13}C NMR (75 MHz, CD_3OD): δ = 11.0, 11.9, 19.2, 23.6, 25.1, 25.3, 39.6, 42.6, 54.7, 56.6.

Anal. Calcd for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.58; H, 9.99; N, 11.48.

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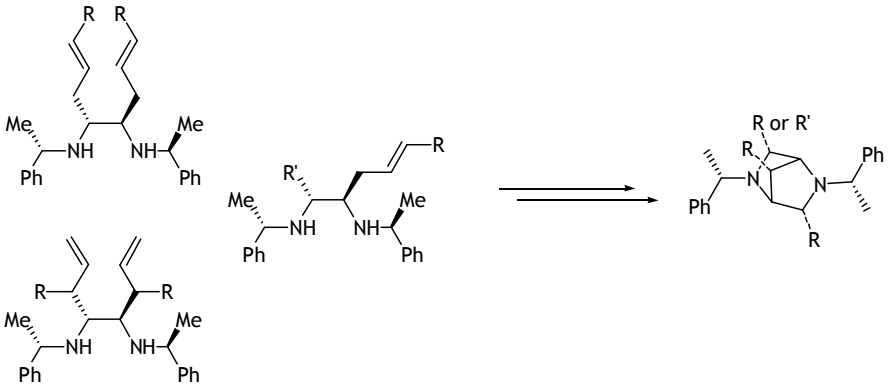
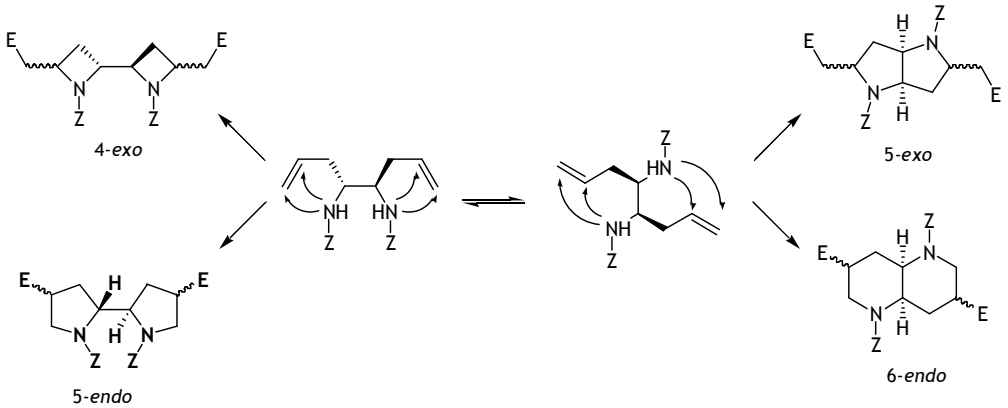
Chapter 3

Iodine-mediated cyclization of chiral 4,5-diamino-1,7-octadienes: A stereoselective route to 2,5-diazabicyclo[2.2.1]heptanes



3.1. Introduction

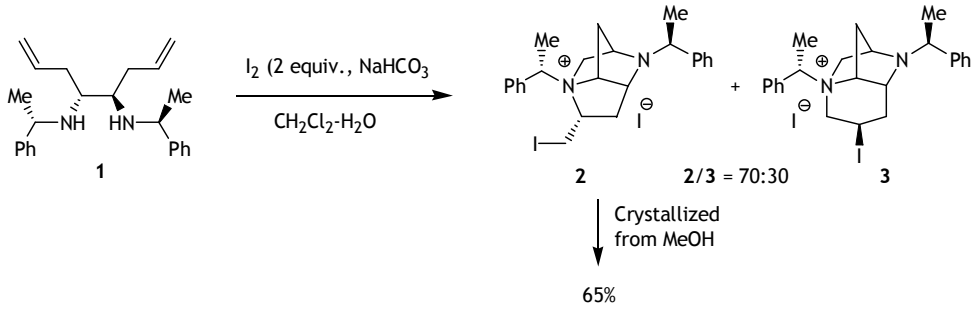
The electophile–mediated cyclization of homoallylic amines is a powerful tool for the construction of aza-heterocycles, so we envisioned that the compound **1**, featuring either the 4- and 5-aminoalkene moieties, could be usefully employed for the synthesis of byciclic aza-heterocycles.[1] In principle, different pathways can be followed by reaction with an electrophile, however, the 5-*exo* cyclization of the two 5-aminoalkene moieties was expected to be preferred with respect to the 4-*exo*- and 6-*endo* cyclizations of the 4- and 5-aminoalkene moieties, respectively, according to the Baldwin's rules for ring closure [2] .

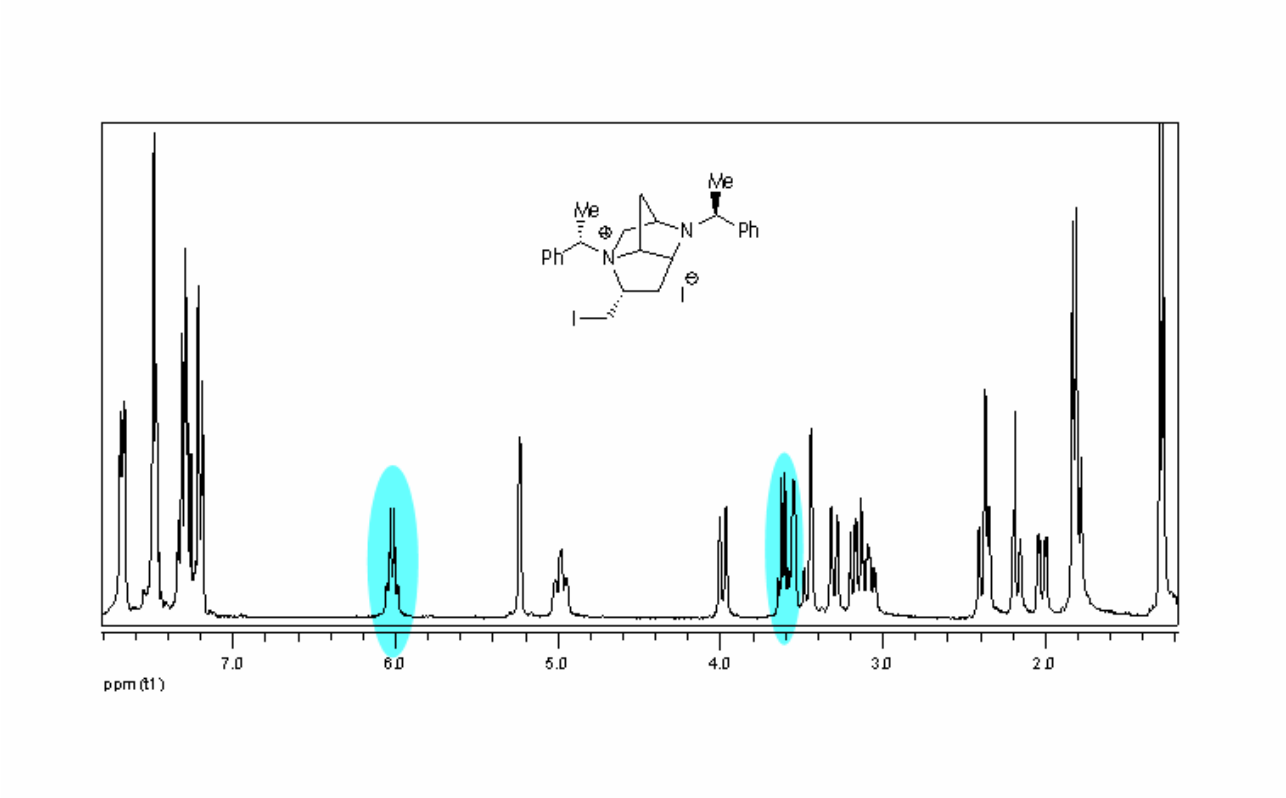


3.2. Iodine-mediated cyclization of (4R,5R)-4,5-di[(S)-1-phenylethylamino]-1,7-octadiene

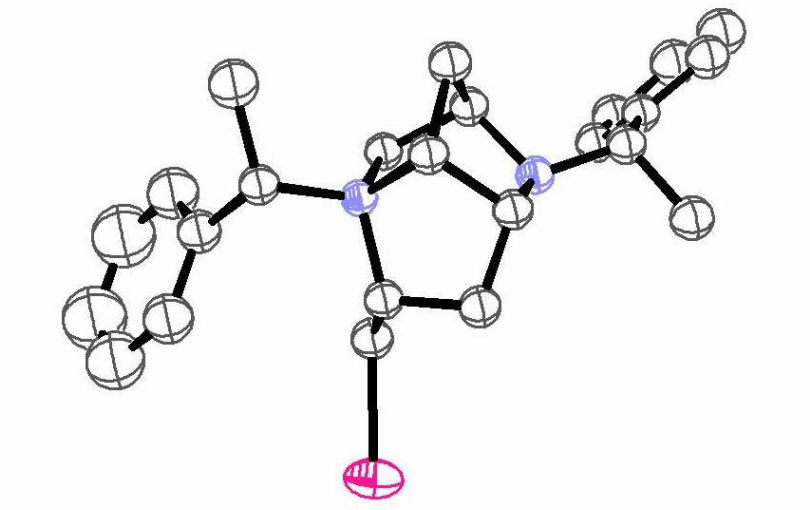
By analogy with reported procedures for the cyclization of unsaturated primary, secondary and tertiary amines, involving treatment with iodine or *N*-iodosuccinimide,[3] we carried out the reaction of the prototypical diaminodiene **1** with two equivalents of iodine in the biphasic system dichloromethane/aqueous sodium hydrogencarbonate. A mixture of two polar products was observed by TLC. They partially decomposed during the GC-MS analysis. Moreover, concentration of the organic solution at reduced pressure led to the isolation of a dark and thick residue, unless the bath temperature was kept below 30 °C. By taking this precaution, a light yellow solid was obtained with almost quantitative yield. ^{1}H NMR analysis of the crude product showed that it was mainly composed of two compounds in a 70:30 ratio. After dissolving the crude reaction product in methanol the prevalent compound **2** precipitated as a white powder and was separated by filtration. After concentration of the mother liquor, the other, more polar compound **3** was isolated almost pure with low yield by column chromatography.

The ^{1}H NMR spectra of the separated compounds gave interesting indications. First, for both compounds a surprising difference in the chemical shifts of the methine protons in the two *N*-substituents was observed: in fact, one methine hydrogen was detected at 6.12 ppm, suggesting that the group was bound to a positively charged, quaternary nitrogen atom (also confirmed by means of ^{1}H- and ^{15}N HNMQC NMR experiments). Moreover, the presence of only one iodine-bearing carbon was observed in both compounds, for which elemental and MS analyses (m/z 473) gave identical results, suggesting that they were isomers.





At first, attempts to obtain crystals of the main compound suitable for X-ray structure determination by crystallization in different solvents proved unsuccessful. By chance, small crystals were observed after a few months in a residue coming from one of those attempts, although the original solvent was unknown. The X-ray analysis (Figure 1) showed the structure of the ammonium iodide **2**, with the fused diazatricyclic skeleton and a *C*-iodomethyl substituent besides the *N*-substituents.



On the other hand, the structure of the minor product **3** as well as the configuration of the iodo-substituted carbon were evinced by NMR studies. The COSY, HSQC, and CIGAR-

HMBC experiments were in agreement with the proposed structure. The ROESY data, compared also with those of compound **2**, indicated the reported stereochemistry. Trace amounts of another unidentified compound were detected in the ^{1}H NMR spectrum of a chromatographic fraction mainly containing **3**.

Treating both salts **2** and **3**, or the crude mixture of them, with organometallic reagents caused the iodine/metal exchange and subsequent β-cleavage of the intermediate organometallic reagent, i.e. the reversal of the alkene iodoamination step (Table 1). As a matter of fact, using isopropylmagnesium chloride at −30 °C, the lowest temperature allowing dissolution of **2** in tetrahydrofuran, we obtained the compound **9**, featuring the 2,5-diazabicyclo[2.2.1]heptane ring, with high yield. The bridged bicyclic structure of **4** was confirmed by ^{1}H NMR investigation. The same product resulted from the crude mixture of **2** and **3** by treatment with *n*-butyllithium and lithium aluminum hydride. On the other hand, the reaction with magnesium turnings, activated with a catalytic amount of iodine in THF, was sluggish.

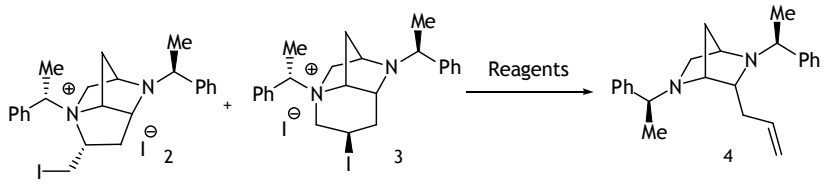


Table 1. Conversion of **2,3** to the bridged pyridazine **4**.

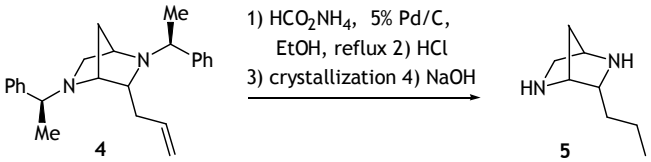
Substrate	Reagents (molar equiv.)	Conditions	Yield (%)[a]
2	*i*-PrMgCl (2.2)	THF, 0 °C, 1 h[b]	90, 68[c]
2	*n*-BuLi (2.2)	THF, 0 °C, 1 h	97, 80[c]
2,3[d]	*n*-BuLi (2.5)	THF, 0 °C, 1 h	97
2,3[e]	$LiAlH_4$ (1)	THF, 0 °C, 1 h	82
2	Zn (3)	THF, AcOH	95
2,3[e]	Bu_3SnH (2.5), Et_3B (2.5)	THF, -30 °C, 3 h	80[f]
2	$Cr(OAc)_2$ (5), *t*BuSH (5)	THF, 25 °C	71[f]
2	$Na_2S_2O_4$ (4)[g]	MeOH-H_2O-DMF	69

[a] Yield of crude product, >95% pure by ^{1}H NMR analysis.
[b] The same result was obtained at -30 °C.
[c] After crystallization (MeOH) of the crude product.
[d] Ratio **10a**/**10b** = 35:65.
[e] Ratio **10a**/**10b** = 65:35.
[f] After chromatography (SiO_2) of the crude product.
[g] In the presence of $NaHCO_3$ (10 equiv.).

In the attempt to avoid the β-cleavage of the β−iodoammonium function and preserve the tricyclic skeleton, we tried the reductive deiodination of **2** by methods not involving the formation of an organometallic reagent by iodine-metal exchange, for example, by treatment with zinc in tetrahydrofuran-acetic acid[4] and lithium aluminum hydride.

However, in all cases the partial or almost complete conversion to **4** was again observed (Table 1). Particularly, the result of the latter reaction is in contrast with the successful reduction of β-bromoamines by the same hydride, where no competing elimination was observed. 7 [3b-e] Even more surprisingly, we observed the complete conversion of **2/3** to **4** using tributyltin hydride and triethylborane[5] (2.5 equivalents each) in tetrahydrofuran at −30 °C, a procedure that proceeds by a radical pathway[6] and was successfully employed to reductively de-iodinate a β-iodoamine.[3] Similarly, the reactions of **2** with chromous acetate/*t*-butyl mercaptan in tetrahydrofuran,[7] and sodium dithionite in methanol-water-dimethylformamide[13 8] followed the same pathway with slightly less efficiency. Moreover, hydrogenation of **2** with common palladium catalysts in different experimental conditions gave complex mixtures of products, in some cases containing **4** with low yields (GC-MS and NMR analyses), but the results were not reproducible and in no case the desired reductive deiodination occurred to a significant extent. These results are in contrast to the results of the palladium-mediated hydrogenolysis of both N-benzyl and C-I bonds of a β-iodoalkylamine.[3] These reactions imply the fragmentation of the β-ammonium radical derived from the salts **2/3**. To the best of our knowledge, fragmentation of an ammonium salt by the unambiguous generation of a β-carbon radical has not been reported in the literature.[9]

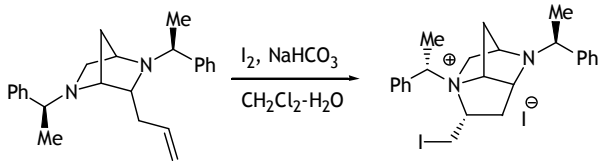
Hydrogenolysis of the benzylic *N*-substituents in **4**, with concomitant hydrogenation of the C=C bond, was easily accomplished by treatment with ammonium formate and 5% palladium on carbon in refluxing ethanol. By this way, the bridged piperazine **5** was obtained in pure state through the dihydrochloride, which was crystallized from a toluene/methanol mixture and then treated with base.



3.3. Mechanism of the iodine-mediated cyclization

In order to assess the effect of different experimental conditions on the reaction outcome and especially to gain information on the reaction pathway/intermediates, further experiments were carried out on the diaminodiene **1**. Repeating the reaction

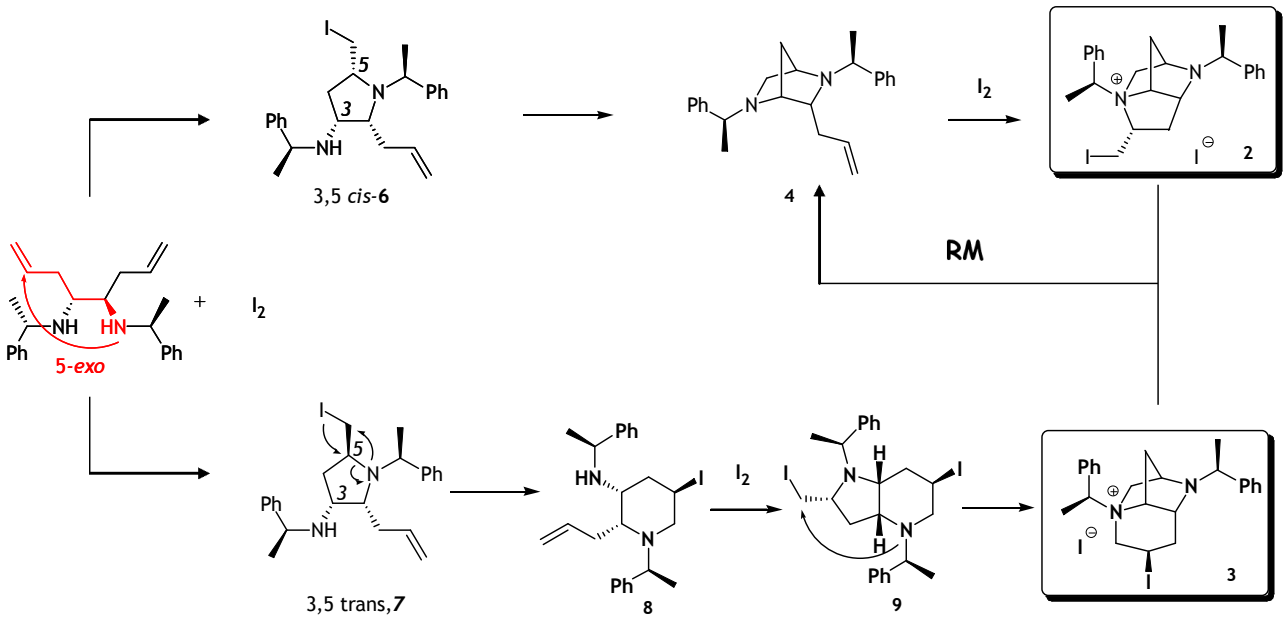
with 2 equivalents of iodine and stirring for a longer time (further 12 h), or heating the reaction mixture at the reflux temperature for 3 h, the composition of the crude reaction mixture did not change. Similarly, by performing the reaction with 2 equivalents of iodine in diethyl ether for 3 h, then adding aqueous sodium hydrogencarbonate to the still coloured solution, the same outcome was observed. Moreover, treatment of the diaminodiene **1** with only one equivalent of iodine gave a mixture of the starting material and products **2/3**, rather than any intermediate. Finally, we carried out the reaction of the allyl-substituted bridged piperazine **4** with one equivalent of iodine and obtained the ammonium iodide **2** as the only product (Scheme 5).



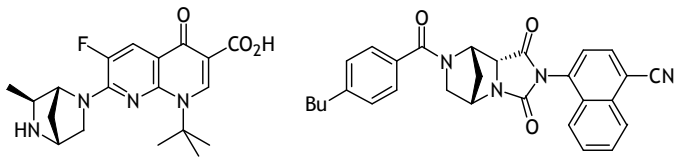
4

2, 100%
Only product

In the light of these and previous results, we suggest that products **2** and **3** are formed from the diaminodiene **1** by the pathways described below. The cyclization of one 5-aminoalkene moiety gives the iodomethylpyrrolidines **6** and **7** through the corresponding diastereomeric iodonium ions or iodine-alkene complexes. It is apparent that **6** is prone to undergo cyclization to give the bridged piperazine **4** by intramolecular substitution of the primary iodide by the secondary amine. Then, a second iodoamination step from **4** leads to the ammonium ion **2**. On the other hand, **7** undergoes a stereospecific rearrangement to give the iodopiperidine **8**. This ring expansion of 2-halomethyl and 2-hydroxymethylpyrrolidines, occurring via aziridinium intermediates, has been described in the literature.[7j,15] [3] [10] This is followed by a second iodo-amination step of the residual 5-aminoalkene moiety, so affording the fused pyrrolidino-piperidine **9**. Then, the ammonium salt **3** is formed from **4** by intramolecular substitution.

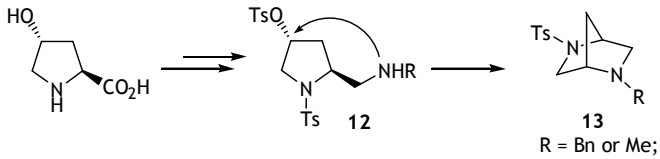


It is worth mentioning that **4** and **5** posses the 2,5-diazabicyclo[2.2.1]heptane skeleton that has been incorporated in a variety of medicinal agents[11] like **10** and **11** to achieve enhanced microbiological activity, due to the increased rigidity with respect to the simple piperazine ring.



10 **11**

Compounds **13** and their analogues with different *N*-substituents, as well as their enantiomers, have been prepared from (*S*)- and (*R*)-4-hydroxyproline, through the intermediates **12** which undergo cyclization by intramolecular S_N2 reaction at 80-110 °C.[12]



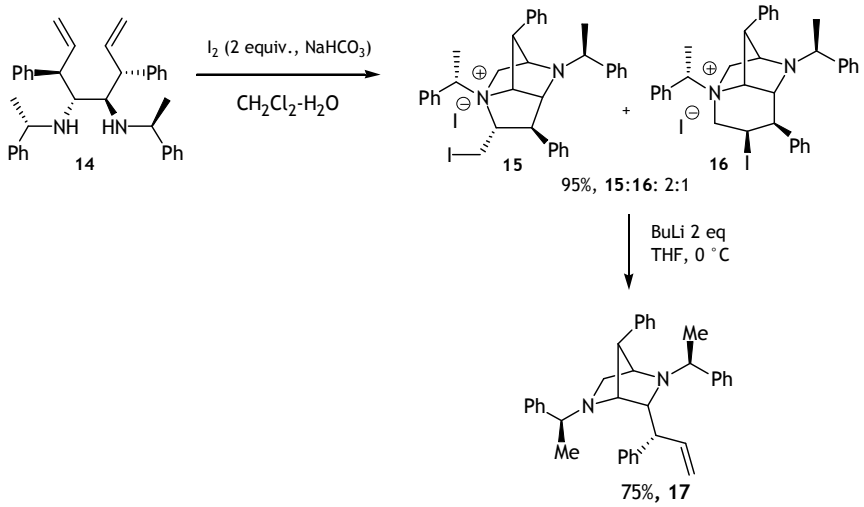
12 **13**
R = Bn or Me;

It should be noted that our route is relatively short and requires milder reaction conditions for the cyclization step, taking advantage of the increased reactivity and

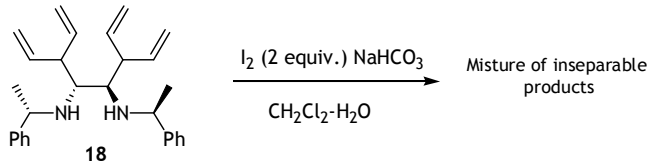
interchanged positions of the iodide and amino functions in the intermediates **5, 6** and **8**, as compared to **12**.

3.4. Iodine-mediated cyclization of 3,6-disubstituted-4,5-diamino-1,7-octadienes

Next step was to verify if the iodine-mediated cyclization could be usefully applied also to substituted diazadienes. We started with the 3,6 diphenyl-substituted diene **14** and used the same reaction protocol, then we again observed the formation of a mixture of two isomeric products **15** and **16** in 2:1 ratio. The ^{1}H-NMR spectrum confirmed that they were quaternary ammonium salts and their structure was assigned by comparison with the previously prepared salts. Any attempts of crystallization did not give any good results, anyway when we treated the crude reaction mixture with buthyllithium in THF at 0 °C we obtained, as expected, the bridged piperazine **17** in very good yield.

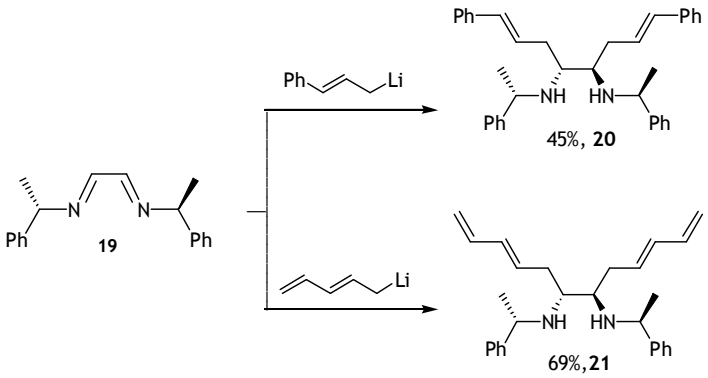


Next, we tested the vinyl-substituted diamine **18** in the same reaction condition, with great disappoint, we observed the formation of mixture of at least four products by TLC analysis. Chromatographyc separation was very difficult, impeding the structural assignments. Changing reaction condition by increasing the temperature, or using an excess of iodine or different solvents had no effect on the outcome of the reaction.

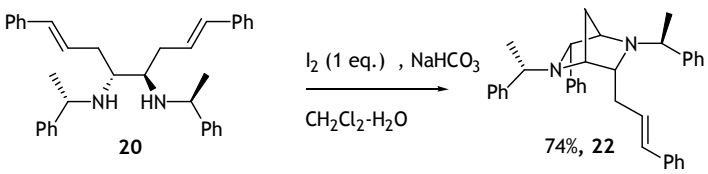


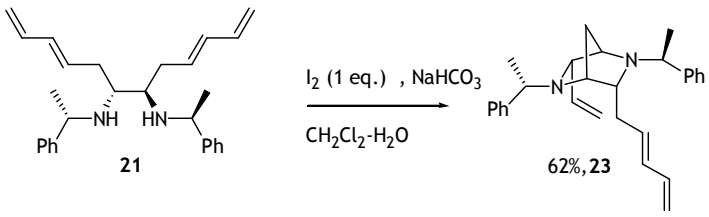
3.4. Iodine-mediated cyclization of 1,8 disubstituted 4,5-diamino-1,7-octadienes

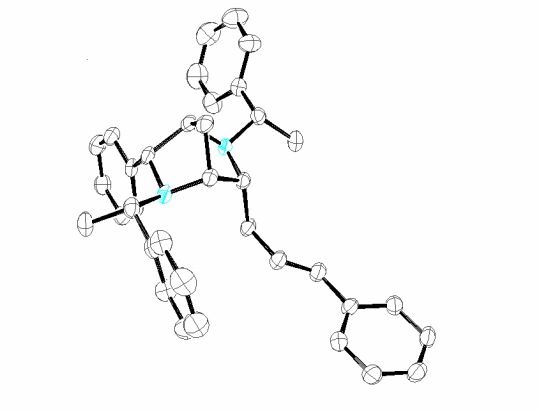
4,5-Diamino-1,8-disubstituted-1,7-octadienes were easily prepared by addition of allylic organolithium reagents to the 1,2-bis-imine **19**. For example, additon of cinnamyllithium and pentadienyllithium proceeded smoothly at –78 °C gave the corresponding linear diamines **20** and **21** with good yields, although with only a modest stereocontrol. The main isomers could be in both cases separated by column chromatography.[13]



Treating the diamine **20** with two equivalents of iodine yielded a major product, as stated by TLC analysis, but from the ^{1}H-NMR spectrum of the crude reaction mixture it was evident that it was not an ammonium salt and that a C=C double bond was still present. After purification by column chromatography and a further crystallization from methanol we obtained crystals suitable for X-ray diffraction analysis, which confirmed the structure of the product as the bridged piperazine **22**. This product is clearly formed by a mechanism analogue to the one above menthioned before but, probably for steric and/or electronic reason, the second iodocyclization step is hampered. Similarly, the reaction of the diamine **21** with iodine gave mainly the bridged piperazine **23**.

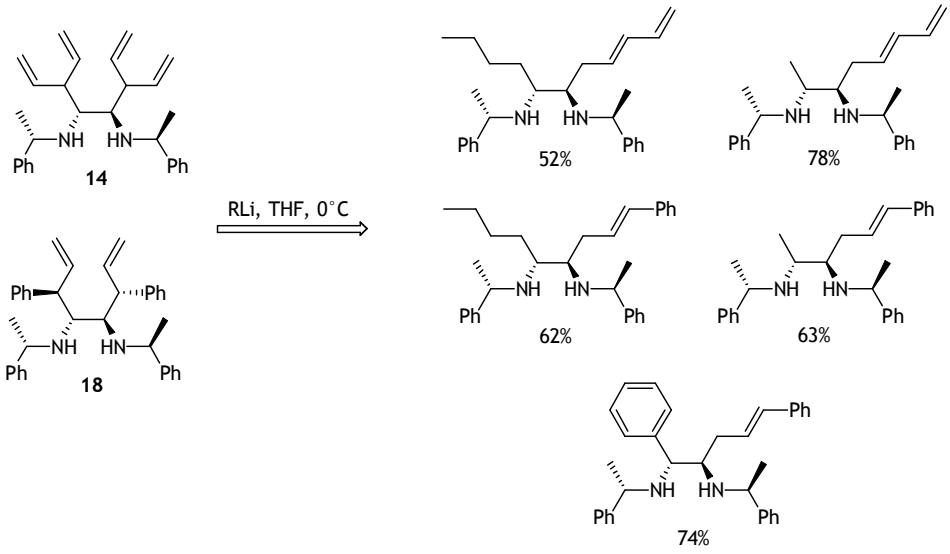




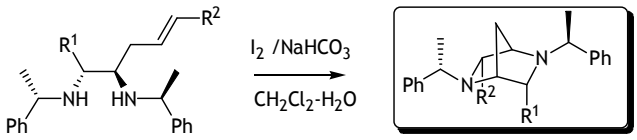


3.5. Iodine-mediated cyclization of 4,5-diamino-1-alkenes

We reasoned that the 2,5-diazabicyclo skeleton would be obtained by iodination of 1,2-diamines bearing only one allylic substituent (4,5-diamino-1-alkenes). A few of such compounds can be easily prepared from the diamines **14** and **18** by reaction with three equivalents of an organolithium reagent in controlled conditions, following a protocol described in the past by our research group[14]. These transformation, displaying high level of stereocontrol, takes place by a complex pathway that involves metalation of one or two N-H bond(s), rearrangement of the branched allylic substituent(s) to the linear one(s), retroallylation of the homallylic moiety to give an intermediate imine, and final addition of the organolithium reagent to this imine.



As expected, treatment of these compounds with only one equivalent of iodine gave the corresponding bridged piperazines with good yields in a single step.



	R^1 = Me	R^1 = *n*-Bu	R^1 = Ph
R^2 = Phenyl	70%, **24**	mixture	61%, **25**
R^2 = Vinyl	68%, **26**	58%, **27**	

Experimental Section

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent in N_2 atmosphere before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), CH_2Cl_2 (P_2O_5). Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR spectra were recorded on Varian Inova and Gemini instruments for samples in $CDCl_3$ which was stored over Mg: ^1H chemical shifts are reported in ppm relative to $CHCl_3$ δ_H 7.27), *J*-values are given in Hz. and in the assignments s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, bm = broad multiplet, dd = doublet of doublets and dt = doublet of triplets. Assignments were assisted with several 2D experiments for structural and stereochemical determinations. Infrared spectra were recorded on a Nicolet FT-210 spectrometer and IR assignments are reported in wavenumbers (cm^{-1}). MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Accurate Mass was determined on an Micromass QTOF2 spectrometer operated in ES ionization mode. Molecular weight was determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. The following materials were purchased from Aldrich: *n*BuLi (2.5 M in hexanes), *i*PrMgCl (2 M in THF), Et_3B (1M in THF), $LiAlH_4$, Zn, Bu_3SnH, $Cr(OAc)_2$, $Na_2S_2O_4$.

4.2. Iodine mediated cyclization of the diaminodiene 1. A solution of I_2 (2.55 g, 10 mmol) in CH_2Cl_2 (50 mL) was slowly added to a magnetically stirred mixture of the diaminodiene **1** (1.74 g, 5 mmol), dissolved in CH_2Cl_2 (15 mL), and sat aq $NaHCO_3$ (30 mL). After stirring was continued for 3 h, decoloration was observed. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were dried over $CaCl_2$ and evaporated at reduced pressure at a temperature <30 °C. The solid pale brownish residue was mainly composed of the two products in a 30:70 ratio by ^1H NMR analysis. However, by dissolving the crude reaction product in MeOH (5 mL) at room temperature, then scratching the walls of the flask with a spatula a white precipitate of **2** was formed, then filtered off, washed with methanol and dried at reduced pressure: 1.60 g (53%). From the mother liquor, a further amount of **2** precipitated and was collected, for a total yield of 1.96 g (65%). Chromatography of the mother liquor, containing **2** and **3** in a 2:1 ratio, on a silica gel column eluting with EtOAc-MeOH mixture (4:1) gave pure fractions of compound **3**, which were collected and concentrated to leave a white solid: 0.122 g (4%).

4.2.1. Ammonium salt 2: m.p. 165-167 °C (dec). $[\alpha]_D^{25}$ +21.4 (*c* 0.69, $CHCl_3$). IR (Nujol): ν_{max} 3400, 1597. ^1H NMR (600 MHz, CDCl3, 25 °C, see Figure for atom numbering): δ 1.29 (d, *J* 6.8, 3 H, H-11), 1.78 (d, *J* 6.5, 3 H, H-13), 2.03 (dd, *J* 3.7, 9.8 Hz, 1 H, H-9), 2.18 (d, *J* 12.4 , 1 H, H-4), 2. 42 (m, 2 H, H-4, H-14), 3.07 (m, 1 H, H-9), 3.17 (dd, *J* 10.7, 7.4, 1 H, H-14), 3.31 (d, *J* 11.3, 1 H, H-6), 3.42 (bs, 1 H, H-5), 3.53 (bs, 1 H, H-2), 3.60 (q, *J* 6.8, 1 H, H-10), 3.86 (dd, *J* 11.3, 1.9, 1 H), 4.98 (m, 1 H, H-8), 5.28 (bs, 1 H, H-3), 6.12 (q, *J* 6.9, 1 H, H-12), 7.20 (d, 2 H. Ph), 7.27 (t, 1 H, Ph), 7.32 (t, 2 H, Ph), 7.47-7.51 (m, 3 H, Ph), 7.62 (d , 2 H, Ph). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ 3.0, 17.3, 22.1, 33.9, 38.3, 56.2, 61.0, 62.7, 64.7, 72.01, 76.8, 81.5, 126.8, 126.8, 127.9, 129.0, 129.0, 129.2, 129.2, 129.9, 129.9, 131.0, 134.1, 143.7. ES MS (*m*/*z*) 473 ($C_{24}H_{30}IN_2^+$). Anal. Calcd for $C_{24}H_{30}I_2N_2$ (600.32): C, 48.02; H 5.04; N 4.67. Found: C, 48.18; H, 5.08; N 4.60.

4.2.2. Ammonium salt 3: mp 139-141 °C (dec). $[\alpha]_D^{25}$ +3.2 (*c* 0.30, $CHCl_3$). IR (Nujol): ν_{max} 3422, 1620, 1279, 1230, 1038, 706. ^1H NMR (600 MHz, $CDCl_3$, 25 °C, see Figure for atom numbering) δ 1.26 (d, *J* 6.5 Hz, 3 H, H-12), 1.78 (d, *J* 7.5, 3 H, H-14), 1.86 (t, *J* 12.9, 1 H, H-10), 2.09 (m, 1 H, H-4), 2.47 (d, *J* 12.9, 1 H, H-10), 3.11 (bs, 1 H, H-2), 3.33 (d, *J* 12.4, 1 H, H-4), 3.38 (t, *J* 12.6, 1 H, H-8), 3.54-3.65 (m, 4 H, H-3, H-5, H-6, H-11), 4.09 (m, 1 H, H-8), 4.46 (bd, *J* 11.3, 1 H, H-6), 4.84 (m, 1 H, H-9), 5.89 (q, *J* 7.5, 1 H, H-13), 7.23-7.29 (m, 3 H, Ph), 7.32 (t, 2 H, Ph), 7.49-7.57 (m, 5 H, Ph). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ 10.0, 14.7, 22.2, 33.7, 38.9, 57.2, 60.1, 61.8, 63.4, 68.6, 70.1, 73.7,

126.9, 126.9, 127.9, 129.0, 129.0, 129.7, 129.7, 130.8, 130.8, 131.2, 132.0, 143.6. ES MS (*m*/*z*) 473 ($C_{24}H_{30}IN_2^+$). Anal. Calcd for $C_{24}H_{30}I_2N_2$ (600.32): C, 48.02; H 5.04; N 4.67. Found: C, 48.21; H, 5.10; N 4.58.

Preparation of (1*R*,3*R*,4*R*)-2,5-di[(*S*)-1-phenylethyl)]-3-(2-propenyl)-2,5-diazabicyclo[2.2.1]heptane (4).

Reaction of 2 with isopropylmagnesium chloride: To a solution of **2** (1.80 g, 3 mmol) in dry THF (30 mL) cooled to 0 °C under Ar atmosphere was added *i*PrMgCl (2 M in THF, 3.3 mL, 6.6 mmol) over 5 min while stirring. After 1 h, the mixture was quenched with sat. aq $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were dried over anhydrous $CaCl_2$ and concentrated to leave **9** as an off-white solid (1.02 g, 2.95 mmol, 98%), which was crystallized from MeOH: white needles, 0.71 g (2.05 mmol, 68%); m.p. 71-72 °C. $[\alpha]_D^{25}$ -101.4 (c 0.4, $CHCl_3$). IR (Nujol): ν_{max} 1635, 1598, 1299, 1213, 1103, 1095, 913, 770, 700. ^{1}H NMR (500 MHz, 25 °C) δ 1.21 (d, *J* 6.5 Hz, 6 H; 2 × CH3), 1.35 (bm, 2 H), 2.20 (bm, 1 H), 2.28 (dd, *J* 3.10 and 9.48, 1 H), 2.32 (dt, *J* 5.34 and 10.30, 1 H), 2.81 (d, *J* 9.25, 1 H), 2.87-2.97 (m, 2 H), 2.99 (m, 1 H), 3.30 (q, *J* 6.5, 1 H), 3.35 (q, *J* 6.5, 1 H), 4.93 and 4.81 (m + m, 2 H), 5.45 (m, 1 H), 7.16 – 7.35 (m, 10 H; Ph). ^{13}C NMR (200 MHz, $CDCl_3$, 25 °C) δ 22.5, 23.6, 28.7, 36.5, 59.9, 61.4, 64.5, 64.8, 69.5, 114.9, 126.5, 126.8, 128.1, 137.3, 140.1, 147.1. MS *m*/*z* (EI; GC-MS) 105 (100%), 241 (29), 68 (28), 137 (25), 305 (24), 173 (17), 80 (15), 172 (12), 346 (2, M^+). Anal. Calcd for $C_{24}H_{30}N_2$ (346.24): C, 83.19; H, 8.73; N 8,08. Found: C, 83.28; H, 8.78; N, 8.02.

Reaction of 2 with *n*-butyllithium: The reaction was performed as in the above described experiment using *n*BuLi (2.5 M in hexanes, 2.4 mL, 6 mmol) to give crude **4** (1.01 g, 97%). Crystallization from MeOH gave pure **4**: 0.83 g (80%). The reaction of the mixture **7/8** (35:65 ratio) with *n*BuLi (2.5 equivalents) gave crude **4** in 97% yield.

Reaction of 2 with zinc-acetic acid: Zinc powder (0.59 g, 9 mmol) was flamed under a stream of argon, then cooled and covered with dry THF (10 mL). Glacial AcOH (5 mL) was added, followed by **2** (1.80 g, 3 mmol), and the mixture was magnetically stirred for 3 h, after which time 40% NaOH was carefully added until pH 11. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the collected organic layers were washed with brine (10 mL), dried over $CaCl_2$ and concentrated to leave crude **4** as an off-white solid: 0.99 g, (95%).

Reaction of 2 with lithium aluminum hydride: $LiAlH_4$ (0.126 g, 3 mmol) was added to a stirred solution of **2** (1.80 g, 3 mmol) in THF (25 mL) at 0 °C under Ar atmosphere. After 1 h, the mixture was quenched with sat aq $NaHCO_3$ (10 mL) and stirred for a further 1 h. The organic phase was extracted with CH_2Cl_2 (3 × 20 mL) and the collected organic layers were washed with brine (10 mL), dried over $CaCl_2$ and concentrated to leave **4** as an off-white white solid: 0.85 g (82%).

Reaction of 2 with tributyltin hydride/triethyl borane/oxygen: Oxygen was bubbled for 2 min through a mixture of **2** (1.20 g, 2 mmol), Bu_3SnH (1.73 g, 6 mmol) and Et_3B (1 M in THF, 4.2 mL, 4.2 mmol) in THF (30 mL) cooled at –30 °C. The mixture was stirred for 3h, then quenched with saturated aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were washed with brine (20 mL), dried over $CaCl_2$ and concentrated to leave a crude oil, which was subjected to chromatography on a silica gel column, eluting with cyclohexane/EtOAc 10:1, to give **4** as an off-white solid: 0.55 g (80%).

Reaction of 2 with chromous acetate/*t*-butylmercaptan: To a solution of **2** (1.20 g, 2 mmol) in THF (30 mL) under an Ar atmosphere were added in order *t*BuSH (1.80 g, 20 mmol) and freshly prepared $Cr(OAc)_2$ (1.11 g, 10 mmol). The mixture was magnetically stirred for 15 h, then quenched with water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were washed with brine (10 mL), dried over $CaCl_2$ and concentrated to leave a crude oil, which was subjected to chromatography on a silica gel column, eluting with cyclohexane/EtOAc 10:1, to give **4** as an off-white solid: 0.49 g (71%).

Reaction of 2 with sodium dithionite: To a mixture of solvents: DMF (8 mL), water (8 mL) and MeOH (12 mL) were added sequentially **2** (0.98 g, 2 mmol), $NaHCO_3$ (1.68 g, 20 mmol) and Na_2S2O_4 (1.54 g, 8 mmol) and the mixture was magnetically stirred overnight. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with brine (3 × 50 mL), dried over $CaCl_2$, then concentrated to leave **4** as an off-white powder: 0.48 g (69%).

Preparation of (1*R*,3*R*,4*R*)-3-propyl-2,5-diazabicyclo[2.2.1]heptane (5). A mixture of **4** (1.04 g, 3 mmol), NH_4HCO_2 (1.80 g, 27 mmol) and 5% Pd/C (0.45 g) in EtOH (40 mL) was heated at reflux temperature for 2 h, then cooled and the solid was filtered off. 37% HCl (0.5 mL, 6.5 mmol) was added to the solution, which was then concentrated at reduced pressure. Toluene (10 mL) and EtOH (10 mL) were added to the residue and the solution was concentrated. The operation was repeated to leave the salt **5-2HCl** as an off-white solid (0.62 g), which was crystallised from toluene-EtOH mixture (4:1): 0.48 g

(76%); m.p. 289-291 °C (dec.). $[\alpha]_D$25 –28.7 (c 0.6, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, DMSO-d_6) δ 0.88 (t, *J* 7.2, 3 H, CH3), 1.34 (m, 2 H, $CH_2CH_2CH_3$), 1.76 (m, 2 H, $CH_2CH_2CH_3$), 2.04 (m, 2 H, $CHCH_2CH$), 3.54 (m, 2 H, NCH_2), 3.62 (m, 1 H, $CHCH_2CH_2$), 4.34 (s, 2 H, $CHCH_2CH$), 9.0–11.0 (bm, 2 × NH_2^+). The free base **5** was obtained from the salt (400 mg, 1.88 mmol) by treatment with 20% aq NaOH (2 mL) and extraction with CH_2Cl_2 (10 × 3 mL), drying the collected organic layers over $CaCl_2$ and concentration: brownish oil, 0.164 g (62%). $[\alpha]_D^{25}$ –45.2 (c 0.6, $CHCl_3$). IR (neat): ν_{max} 3443, 3264, 1261, 1169, 1116, 1063, 957, 751. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ 0.94 (t, *J* 7.2, 3 H, CH_3), 1.20-1.60 (m, 4 H, $CH_2CH_2CH_3$), 1.76 (m, 2 H, $CHCH_2CH$), 1.82 (bs, 2 H, NH), 2.70 (d, *J* 9.8, 1 H, NCH_2), 2.97 (dd, J_1 2.2, J_2 9.8, 1 H, NCH_2), 3.12 (dt, J_1 1.4, J_2 6.8, 1 H, $CHCH_2CH_2$), 3.37 and 3.52 (2 s, 2 H, $CHCH_2CH$). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C) δ 14.0, 20.1, 34.2, 38.6, 53.9, 56.7, 57.7, 62.3. MS *m/z* (EI, GC-MS): 68 (100%), 69 (56), 98 (44), 140 (M^+, 22), 82 (19), 56 (11), 111 (10), 125 (M^+ - CH_3, 3). HRMS *m/z* calcd for $C_8H_{17}N_2$ (MH^+): 141.1392, found 141.1392.

Ammonium Salt 15: $[\alpha]_D^{25}$ +61.8 (c 0.65, CHCl3); IR: 2960, 2867, 2362, 1454, 1060, 703. 1H NMR (300 MHz, 20 °C): δ = 1.05 e 1.12 (2 d, *J* = 6.7 Hz, 6 H; CH3-z e CH3-v), 1.85 (d, *J* =6.8 Hz, 1 H; *CH*Ph), 3.03 (q, J = 6.7 Hz, 1 H, N*CH*Ph), 3.48 (dd, *J* = 7.8 Hz, 1 H), 3.68 (q, *J* = 10.1 Hz, 1 H), 3.91 (m, 3 H), 4.65 (m, 1 H), 4.96 (dd, *J* = 11.1 Hz e *J* = 17.2 Hz, 2 H; N^+CH_2), 5.98 (q, *J* = 5.8 Hz, 1 H, N^+CH), 6.29 (d, *J* = 6.7 Hz, 1 H; N^+CH), 6.90 (m, 5 H; Ph), 7.00 (m, 5 H; Ph), 7.20 (m, 5 H; Ph), 7.50 (m, 5 H; Ph). C^{13} NMR (75 MHz, $CDCl_3$): δ= 14.7, 17.7, 24.3, 27.1, 49.7, 56.4, 59.720, 67.3, 70.1, 70.3, 126.5,129.5, 143.5.

Bridged piperazine 17: $[\alpha]_D^{25}$ +41.7 (c 1.06, CHCl3); IR: 2958, 2928, 1948, 1875, 1801, 1451, 759. 1H NMR (300 MHz, 20 °C): δ = 0.29 (d, *J* = 6.2 Hz, 3 H; CH*Me*), 1.34 (d, *J* =7.3 Hz, 3 H; CH*Me*), 2.63 (dd, J = 8.4 e 2.4 Hz, 1 H, N*CH*), 3.04 (q, *J* = 6.2 Hz, 1 H, N*CH*Ph), 3.16 (d, *J* =8.0 Hz, 1 H,Ph*CH*CH=CH_2), 3.32 (bs, 1 H,), 3.55 (bs, 1 H), 3.55 (q, *J* =7.3 Hz, 1 H, N*CH*Ph), 3.62 (bs, *1* H), 4.30 (q, *J* = 6.7 Hz, 1 H), 5.04 (dd, *J* = 10.0, 17,1 Hz, 2 H, CH=CH_2), 6.50 (ddd, *J* = 8.0, 10.0, 17,1 Hz, 1 H; CH*CH*=CH_2), 6.90 (m, 5 H; Ph), 7.00 (m, 5 H; Ph), 7.20 (m, 5 H; Ph), 7.50 (m, 5 H; Ph). C^{13} NMR (75 MHz, $CDCl_3$) δ 21.2, 48.7, 60.311, 62.5, 63.8, 64.3, 65.4, 114.956, 125.6, 140.0, 140.3, 143.8, 144.5, 148.5.

Bridged piperazine 22: m.p. 59-61 °C; $[\alpha]_D^{25}$ -11 (c 0.75, $CHCl_3$); IR: 2925, 2850, 1492, 1450, 1100, 968, 749, 701. ^{1}H NMR (300 MHz, $CDCl_3$): □ = 1.12 (d, *J* = 6.5 Hz, 3 H, CH*Me*), 1.20 (d, *J* = 6.7 Hz, 3 H, CH*Me*), 1.64 e 1.81 (dd, *J* = 9.8 e 1.6 Hz, 1 H, NCHCH_2CHN), 2.37 (dt, *J* = 10,3 e 2.5 Hz, 1 H, CHCH_2CH=CH), 2.52 (dt, *J* =10,3 e 2.5 Hz, 1 H, N*CH*CH)

3.19 (s, 1 H, N*CH*CH), 3.27 (s, 1 H, NCHCH), 3.38 (q, *J* = 6.5 Hz, 1 H, N*CH*Me), 3.46 (m, 1 H, CH2CH=CH_2), 3.62 (q, *J* = 6.7 Hz, 1 H, N*CH*Me), 3.81 (d, *J* = 2.5 Hz, 1 H, N*CH*(Ph)CHN), 5.80 (ddd, *J* = 15.8, 10,3 e 2.5 Hz, 1 H, *CH*=CHPh), 6.38 (d, *J* = 15.8 Hz, 1 H, CH=*CH*Ph), 6.69-7.53 (m, 20 H, Ph).

C^{13} NMR (75 MHz, $CDCl_3$): ¤ 23.9, 23.478, 31.8, 34.1, 62.8, 64.6, 65.2, 67.1, 70.4, 73.6, 125.8, 129.2, 130.0, 137.8, 143.0, 146. 4.

Bridged piperazine 23: $[\alpha]_D^{25}$ 49.8 (c 0.60, $CHCl_3$); IR:3024, 2971, 2010, 1960, 1903, 1451, 1301, 1101, 1003, 910, 766, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ =.1.34 1.35 (d, 2 H, CH*Me*), 1.55 (bs, 2 H, NCHCH_2CHN) 2.36 (dt, *J* = 9.6 2.5 Hz, 1 H, NCHCH_2), 2.54 (dt, *J* = 10.3 2.5 Hz, 1 H, N*CH*CH_2), 3.08 (bs, 1 H, N*CH*CH_2) 3.12 (bs, 1 H, N*CH*CH_2) 3.14 (bs, 1 H, N*CH*CH=CH_2), 3.26 (m, 1 H, *CH2*CH=CH), 3.50 (q, *J* = 6.2 Hz, 1 H, N*CH*Me), 3.59 (q, *J* = 6.3 Hz, 1 H, N*CH*Me), 5.00 (dd, 2 H, CH=CH_2), 5.20 (dd, 2 H, CH=CH_2),

5.39 (ddd, *J* = 6.3, 8.0, 15,1 Hz, 1 H, *CH*=CH_2), 6.18 (m, 2 H, CH=*CHCH*=CH_2), 6.44 (m, 1 H, *CH*=CHCH=CH_2), 7.26-7.46 (m, 10 h, Ph).

C^{13} NMR (75 MHz, $CDCl_3$): δ 23.5, 24.4, 31.3, 34.5, 63.1, 65.1, 65.3, 66.9, 70.3, 72.6, 114.8, 115.1, 127.2, 127.4, 128.9, 132.3, 135.2, 142. 7, 145, 5, 146.8.

Bridged piperazine 25: $[¤]^{20}_D$ ~25.9 (c 0.38, $CHCl_3$); IR: 2927, 1954, 1900, 1840, 1496, 1450, 1262, 1089, 739, 704. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.7 Hz, 6 H, CH*Me*), 1.81 (d, *J* = 1.1 Hz, 2 H, CHCH_2), 3.4 (q, *J* = 6.7 Hz, 2 H, N*CH*Me), 3.45 (s, 2 H, *CH*CH_2), 3.77 (s, 2 H, NCHPh), 6.84-7.12 (m, 10 H, *Ph*), 7.27 (m, 5 H, Ph).

C^{13} NMR (75 MHz, $CDCl_3$): δ = 23.6, 32.1, 65.2, 67.7, 73.2, 76.4, 126.0, 129.2, 126.9, 127.6, 128.2, 129.3, 142.3, 146.3.

Bridged piperazine 24: $[\alpha]_D^{25}$ ~-65.0 (c 0.7, $CHCl_3$); IR: 2924, 2852, 1731, 1450, 1372, 1096, 802, 765, 700. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 e 1.16 (2 d, *J* = 6.4 Hz, 6 H, NCH*Me*), 1.44 (d, *J* = 6.1 Hz, 3 H, NCHCH_3), 1.74 (dd, *J* = 9.5 e 24.1 Hz, 2 H, CHCH_2CH), 2.69 (dq, *J* = 2.8 e 6.1 Hz, 1 H, N*CH*CH_3), 3.06 (s, 1 H, *CH*CH_2CH), 3.18 (s, 1 H, CHCH$_2$*CH*), 3.37 e 3.61 (2 q, *J* = 6.6 Hz, 2 H, N*CH*Ph), 3.79 (s, 1 H, N*CH*Ph), 6.72-7.54 (m, 15 H, *Ph*). C^{13} NMR (75 MHz, $CDCl_3$): δ = 17.0, 24.1, 31.5, 63.9, 64.2, 64.8, 65.4, 64.1, 73.3, 125.6, 126.2, 126.6, 127.0, 128.2, 142.7, 146.4.

Bridged piperazine 26: $[\alpha]_D^{25}$ 49.0 (c 0.6, $CHCl_3$); IR: 2921, 2868, 1956, 1879 1801, 1736, 1674, 1446, 1360, 1204, 694. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.5 Hz, 3 H, NCH*Me*), 1.23 (s, 3 H, CHCH_3), 1.26 (d, *J* = 6.1 Hz, 3 H, NCH*Me*), 1.43 (q, *J* = 9.5 Hz, 2 H, CHCH_2CH), 2.56 (dq, *J* = 5.8 e 2.5 Hz, 1 H, *CH*CH_3), 2.84, 2.92 e 2.95 (3 s, 3 H,

N*CH*CH), 3.35 (q, *J* = 6.5 Hz 1 H, N*CH*Ph), 3.47 (q, *J* = 6.1 Hz, 1 H, N*CH*Ph), 5.06 (dd, *J* = 6.2 e 10.1 Hz, 2 H, CH=*CH_2*), 6.30 (ddd, *J* = 6.3, 10.1 e 17.3 Hz, 1 H, *CH*=CH_2); C^{13} NMR (75 MHz, $CDCl_3$): δ =.17.6, 23.5, 23.8, 30.9, 43.3, 64.2, 64.6, 64.7, 65.4, 66.9, 71.0, 97.1, 113.9, 126.4, 126.5, 128.141, 142.1, 147.2, 164.1.

Bridged piperazine 27: $[\alpha]^{D25}$ ¯94.8 (c 0.47, $CHCl_3$); IR: 2941, 2868, 2582, 1952, 1875, 1813, 1446, 1102, 910, 702. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 4 H, *CH_2CH_2*CH_3), 1.20 (t, *J* = 6.6 Hz, 6 H), 1.29 (m, 3 H), 2.32 (m, 2 H, *CH*$CH=CH_2$), 2.93 (s, 1 H, N*CH*), 2.97 (s, 2 H), 3.36 (q, *J* = 6.6 Hz, 1 H, N*CH*Me), 3.46 (q, *J* = 6.4 Hz, 1 H, N*CH*Me), 5.03 (dd, *J* = 10.1 e 9.6 Hz, 2 H), 6.35 (m, 1 H, *CH*=CH2), 7.26 (m, 10 H, *Ph*). C^{13} NMR (50 MHz, $CDCl_3$): δ =.14.362, 23.201, 23.337, 23.800, 27.039, 29.194, 30.446, 30.6, 62.5, 66.6, 70.0, 71.9, 113.9, 126.5, 126.8, 127.5, 127.7, 128.1, 128.2, 142.3, 146.9, 147.1.

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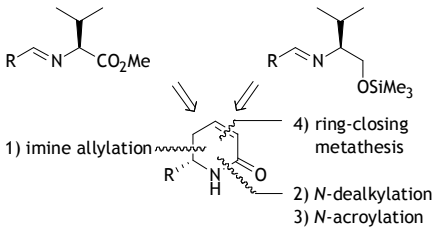
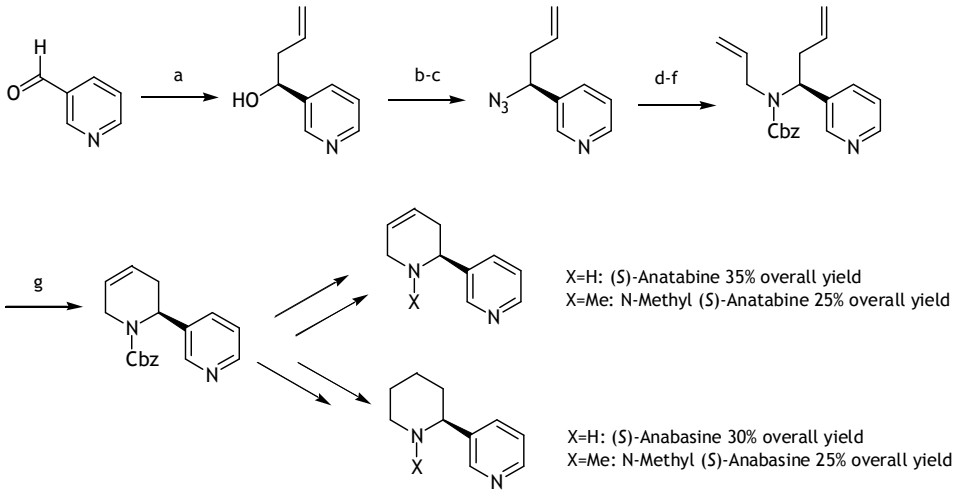
Chapter 4

Asymmetric Synthesis of δ-Substituted δ-Lactams from Imines Exploiting the Ring Closing Metathesis Reaction.



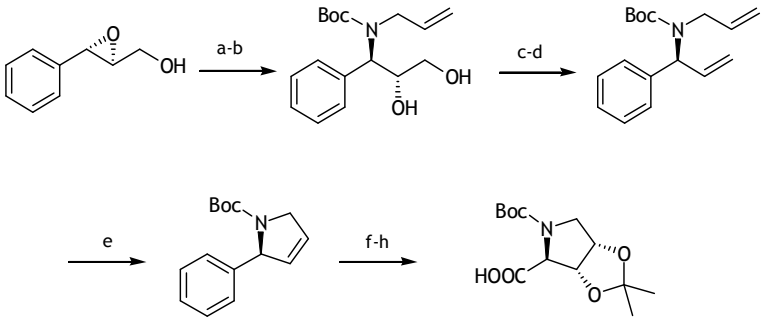
4.1 Introduction

The ring closing metathesis (RCM) of 1,n-dienes is a powerful and versatile tecnique for the construction of carbocyclic and heterocyclic compounds.[1] In particular, this methodology has been exploited for the synthesis of azaheterocycles, as witnessed by several reviews dealing with the synthesis of natural compounds like piperidine and pyrrolidine alkaloids,[2,3] dipeptide mimetics,[4] and β-lactams of non-classical structure.[5] For example, LeBreton et all. employed the RCM reaction to build up the skeleton of four pipecoline alkaloids, In this case the chiral centre was constructed with very high stereocontrol using B-allyldiisopinocampheylborane as the chiral reagent, but the conversion of the hydroxyl moiety to the amine functionality required four further steps[2a].



a) (+)-Ipc_2BAll, Et_2O, 94%, 94% e.e. b) MsCl, TEA, DCM, 100% c) NaN_3, DMF 97% 94% e.e. d)$SnCl_2$ MeOH, 98%
e)BnCOCl, K_2CO_3, DCM 76%, f)NaH, DMF, 76% g) HCl gas. then 1st Gen. Grubbs' Cat. (7.5 mol%), DCM , 79%

Much less work has been devoted to the synthesis of natural pyrrolidine products by application of RCM technology, Riera et al. reported a formal synthesis of (*L*)-3,4-di-hydroxyproline, a natural α-amino acid isolated in 1994, as its protected derivative.[2b] employing a regioselective ring opening reaction of a chiral epoxide (easily available with 99% e.e by Sharpless epoxidation of cinnamyl alchool) as the key step followed by reduction of the diol moiety by the Corey/Hopkins reaction, RCM reaction and an unusual oxidation reaction of the phenyl ring.



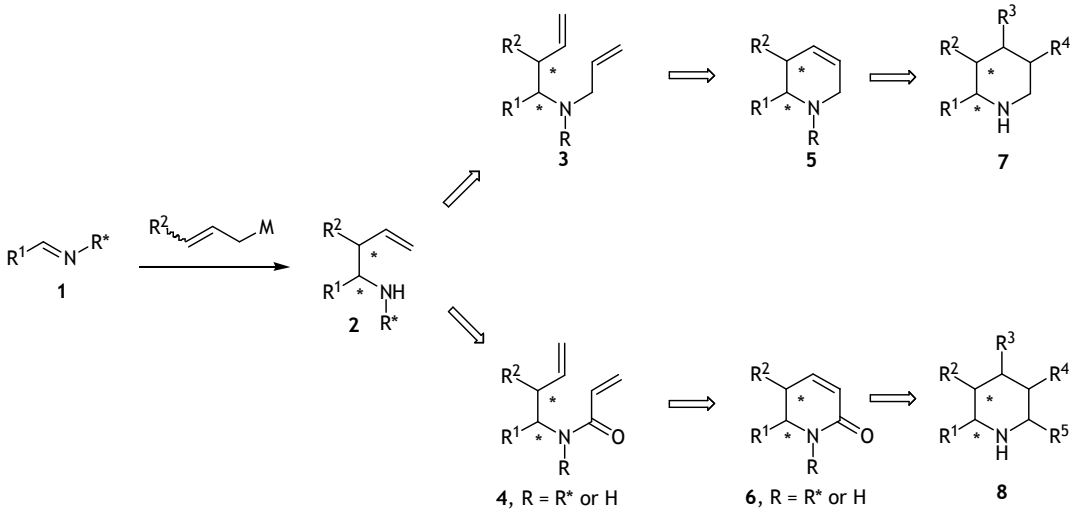
(L)-3,4 N-Boc Dihydroxyproline acetonide,37% overall yield

a) $AllylNH_2$, $Ti(OiPr)_4$, DCM, 97%, b) BOC_2O, $NaHCO_3$, MeOH, c)Cl_2CS, DMAP, DCM, then d) 1,3-dimethyl-2-phenyl-1-3-2-diazaphospholidine, 72% e) 1st Gen. Grubbs' Cat. (5 Mol%), DCM, 99%, f) OsO_4, K_2FeCN_6, K_2CO_3, $tBuOH/H_2O$, 99% g) 2-2-dimethoxypropane, $(CH_3)_2CO$, 96%, h) $RuCl_3$, $NaIO_4$, $NaHCO_3$, CCl_4, CH_3CN, H_2O, 59%

As one can imagine, the required azadiene for the RCM reaction can be prepared by different methodologies. Among the others, a very simple route involves the addition of an unsaturated organometallic reagent to an imine and the subsequent *N*-alkylation with an unsaturated alkyl halide. In this case, the required asymmetric induction in the carbon-carbon bond formation step can be achieved by three different methodologies exploiting: (a) "substrate-induced diastereoselectivity" (SID),[6] where the chirality is present in the imine, generally in the C-substituent, and is retained in the product; (b) "auxiliary induced diastereoselectivity" (AID), where the chirality is present in the imine, generally in the *N*-substituent, that is removed in a successive step; (c) "reagent induced stereoselectivity" (RIS),[7] where the asymmetric induction is provided by a chiral ligand that is bound to the metal by covalent bond(s) or by Lewis acid-base interaction(s).

The AID approach to the synthesis of substituted piperidines is illustrated in the following scheme. It involves allylation of the chiral imine **1** to give the homoallylic amine **2**, and successive N-allylation to give the 5-aza-1,7-diene **3**. The absolute

configuration of the new stereocenter α to the N formed in the allylmetalation step is controlled by the chiral auxiliary (N-substituent). When the allylmetal reagent bears a γ-substituent (R^2), two stereocenters are formed, whose relative stereochemistry is determined by the (*E*) or (*Z*) geometry of the substituted allylmetal reagent. Based on these reports, we considered that there was room for improvement. Above all, we foresaw a significant variant in the synthetic sequence by the conversion of the secondary homoallylic amine **2** to the acryloyl amide **4**, as the N-acryloyl substituent provides at the same time a two carbon fragment to the ring being constructed and acts as a protective group of the amine function in the RCM step leading to the α,β-unsaturated-δ-lactams **6**.[13,14].



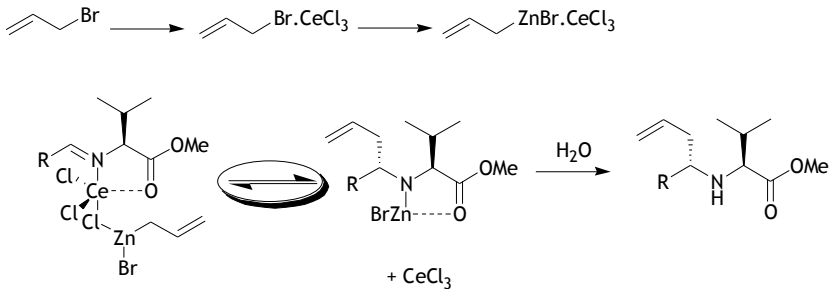
In principle, either the size and/or the position of the double bond of the unsaturated lactams can be varied by the proper choices of the ω-alkenylmetal reagent and the ω-alkenyl/alkenoyl halide. However, the synthesis of six-membered rings takes advantage of the higher reactivity and ready availability of the allylic organometallic reagents and allyl/acryloyl halides. Following the general route described above we studied a synthesis of δ-substituted-α,β-unsaturated-δ-lactams **6** through **4**.[15] It is worthwhile observing that although a great number of methods are available for the synthesis of α,β-unsaturated-δ-lactams,[16] we could find in the literature only few reports of optically pure δ-substituted-α,β-unsaturated-δ-lactams, having R^1 = (*R*)-CO_2Me,[13a] (*S*)-CO_2Me,[16a] R^1 = (*R*)-[(3*R*,5*S*)-1-Cbz-5-(acetoxymethyl)piperidin-3-yl),[13e] R^1 = (*S*)-CH_2CO_2Me,[13k] R^1 = (*S*)-*n*-$C_{15}H_{31}$,[13l] R^1 = (*S*)-CO_2H,[16u] and R^1 = (*S*)-CO_2tBu (*N*-Boc derivative).[16t]

Obviously, the usefulness of our synthetic route is based on the capability to achieve the highest possible diastereoselectivity in the first allylmetalation step. In this respect, the

careful choice of the chiral auxiliary (amine) is the top priority , and should be based on the nature of the starting aldehyde.[17] A variety of optically pure primary amines (including amino acid esters and amides, and β-aminoalcohols), hydrazines, hydroxylamines and sulfinamides are available for this purpose, each of them often provides excellent diastereoselectivity in organometallic additions, particularly with allylmetal reagents, as thoroughly described in recent reviews.[17,18]

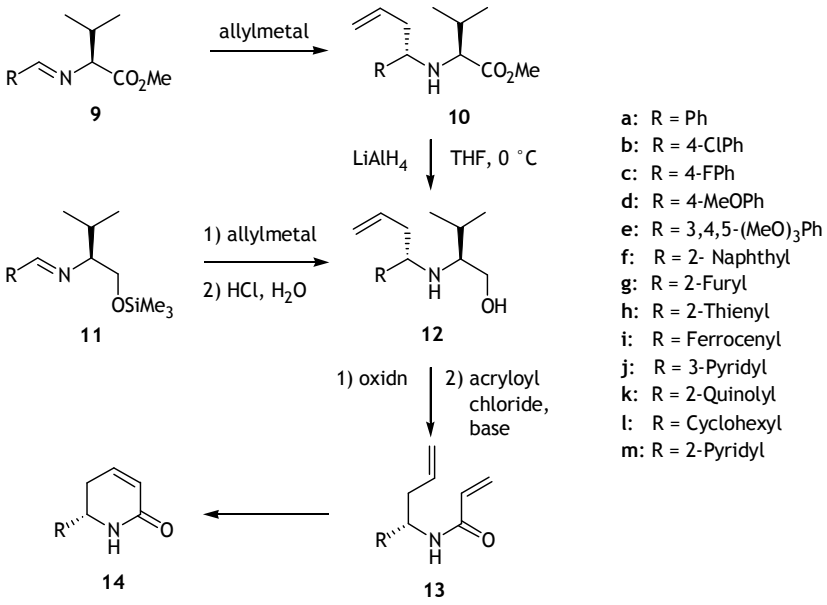
4.2 Results and discussion:

We exploited (*S*)-valine methyl ester as chiral auxiliary for the preparation of the homoallylic amines **13** from the precursor imines **9** since we previously achieved high to complete stereocontrol in this crucial step by the addition of allylcopper, -tin, -lead and -zinc reagents to a variety of aromatic and aliphatic imines in anhydrous tetrahydrofuran at low temperature following the Grignard protocol.[19] We also described a convenient Barbier reaction which relies on the reaction of imines with allyl bromide, zinc and a catalytic amount (generally 10 mol%) of cerium trichloride heptahydrate in anhydrous THF at 0 °C.[9] The hydrated cerium salt may have different roles in the process, but above all it prevents the retroallylation reaction so preserving the stereochemical purity of the homoallylic zinc amide produced. As a matter of fact, almost complete diastereoselectivities were obtained with aromatic and aliphatic imines.

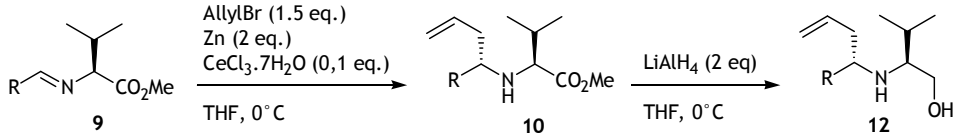


After a seminal paper by our research group, other authors reported that this Barbier protocol worked efficiently and diastereoselectively with substituted allylic bromides and with 4-hydroxybenzaldimine and its *O*-substituted derivatives, suitable substrates for the preparation of supported chiral catalysts.[20] More recently, the same procedure has been efficiently applied to imines derived from 2-thiophenecarboxaldehyde and

several α-aminoacid esters, as well as **9h**; moreover, such addition reactions employing diimines or triimines with a polycyclic aromatic core produced the chiral multiallylic dendritic amines with similar diastereoselectivity.[21] On this basis, we decided to implement the stereoselective synthesis of new homoallylic amines **10b-l** by applying our Barbier protocol to the imines **9b-l**, derived from either aromatic and aliphatic aldehydes. The primary homoallylic amine precursors of **13a-l** were then obtained by the efficient reduction of the ester group by lithium aluminium hydride to give the intermediate amino-alcohols **12** and removal of the *N*-substituent by oxidative procedures.



The results of the Barbier allylmetalation of the imines **9a-l**, derived from valine methyl ester, are reported in the table below. In almost all cases, as expected, we observed complete or almost complete diastereoselectivity (d.r. >99:1) and high yield of the desired homoallylic amines **10**, which were purified from small amounts or traces of starting materials and, especially for the reaction on the *p*-fluorophenylimine **9c**, products coming from overreaction (attack to the ester group). As we observed previously with the corresponding 2-pyridineimine, a low diastereoselectivity was obtained with the 2-quinolineimine **9k** (d.r. 66:34). In this case, no attempt was made to separate the two diastereomers.



Imine 9, R	10	D.r. [c]	Yield (%)	12 from 10 (yield %)[d]
9a, Ph	**10a**	100:0	86	98
9b, 4-ClPh	**10b**	>99:1	78	98
9c, 4-FPh	**10c**	>99:1	80	92
9d, 4-MeOPh	**10d**	>99:1	87	98
9e, 3,4,5-$(MeO)_3$Ph	**10e**	>99:1	76	94
9f, 2-Naphthyl	**10f**	>99:1	91	100
9g, 2-Furyl	**10g**	>99:1	65	92
9h, 2-Thienyl	**10h**	>99:1	86	100
9i, Ferrocenyl	**10i**	>99:1e	80[f]	100
9j, 3-Pyridyl	**10j**	>99:1	88	71
9k, 2-Quinolyl	**10k**	66:34	95g	-
9l, *c*-Hx	**10l**	>99:1	79	90

[a]:The reactions were performed on 5-10 mmol of imine by the Barbier protocol using allylBr (1.5 equiv.), Zn (2 equiv.), $CeCl^3$-$7H^2O$ (0.1 equiv.), THF, 0 °C, 1 h.

[b] Reaction conditions: $LiAlH_4$ (2 equiv. vs **10**), THF, 10 °C, 1 h.

[c] Determined by GC-MS and ^1H NMR analysis of the crude product.

[d] Yield of product isolated by flash chromatography.

[e] The product was not eluted by GC-MS; an impurity, detected in <5% amount by 1H NMR analysis, could not be identified.

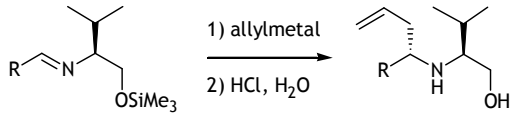
[f] The pure diastereomer was obtained by crystallization of the crude product from MeOH.

[g] No attempt was made to separate the diastereomers.

We previously reported that valine methyl ester is not the best auxiliary for the "Grignard" allylation of *N,N*-bidentate imine; the reaction carried out by the cerium-catalyzed or other Barbier protocols gave even worse results in terms of diastereoselectivity. Instead we found out that *O*-silyl protected (*S*)-valinol was an excellent and convenient chiral auxiliary for the addition of organolithium, Grignard and organozincate reagents to the imines **11**.[22] In particular, it provided better stereocontrol than valine esters for the allylzincation of bidentate imines like those derived from 2-pyridinealdehyde. Protection of the valinol OH group is opportune, otherwise an excess of organometallic reagent, a longer reaction time and higher temperatures are required,

consequently a lower diastereoselectivity is often obtained, as we observed, for example, in the Zn-mediated Barbier reaction on the benzaldimine **10a**.[9a]

It should also be noted that the *O*-silyl protection is easily introduced, as well as easily removed to obtain the secondary homoallylic amines **12** by a simple acidic hydrolysis or treatment with ammonium fluoride in protic solvent, hence it is more conveniently used than the *O*-methyl or *O*–benzyl protections reported by other authors.[13,18] Moreover, the valinol-derived *N*-substituent can be directly removed from the amine **12** by an oxidative cleavage, whereas reduction of the ester group step of the secondary amine **10** is an additional step when starting from the imine **9**. Hence, we carried out the allylmetalation of the 2-quinolineimine **11k** using either allylzinc bromide or allylmagnesium chloride (Table 2). However, the homoallylic amine **12k** was obtained with a diasteromeric ratio not exceeding 90:10 after a routine desilylation step, markedly differing from the almost complete diastereoselectivity obtained for the 2-pyridine derivative **12m**.[22a] The prevalent diastereomer was then isolated in a fair yield by column chromatography.



11 **12**

Imine 11, R	Allylmetal	12	D.r.[b]	Yield (%)[c]
11k, 2-Quinolyl	AllylZnBr	**12k**	80:20	45
11k, 2-Quinolyl	AllylMgCl	**12k**	90:10	45
11m, 2-Pyridyl	AllylMgCl[d]	**12m**	99:1	87

[a] The reactions were performed on 5-10 mmol of imine; allylmetal (2 equiv.), THF, ~78 °C, 3 h.

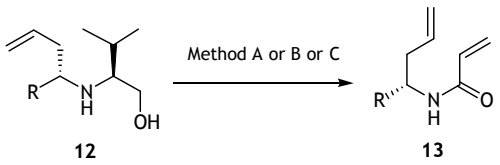
[b] Determined by ^{1}H NMR analysis of the crude product.

[c] Yield of the pure prevalent diastereomer isolated by column chromatography

[d] Reaction described in ref. 22a.

The diastereomerically pure β-aminoalcohols **12** were then subjected to cleavage of the auxiliary group (*N*-substituent) by an oxidative protocol using aqueous periodic acid in the presence of methylamine. The crude primary homoallylic amines were not purified but directly converted to *N*-acryloyl amides **13** by routine procedures using acryloyl chloride and different bases: sodium carbonate in acetone (procedure A) or triethylamine in dichloromethane with a catalytic amount of 4-dimethylaminopyridine

(procedure B). Only in the case of the aliphatic amine **12l** the cleavage of the *N*-substituent was preferably achieved with lead tetraacetate/hydroxylamine hydrochloride and the primary amine was then reacted with acryloyl chloride/sodium carbonate/acetone (procedure C). By these two-step procedures the unsaturated amides **13** were obtained with good overall yields (Table 3).

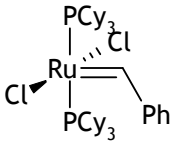


12 **13**

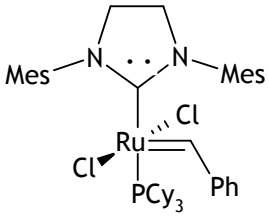
Compound 12, R	Method[a]	Product 15	Yield (%)[b]
12a, Ph	A	**15a**	74
12b, 4-ClPh	A	**15b**	75
12c, 4-FPh	A	**15c**	78
12d, 4-MeOPh	A	**15d**	87
12e, 3,4,5-$(MeO)_3$Ph	A	**15e**	77
12f, 2-Naphthyl	A	**15f**	90
12g, 2-Furyl	B	**15g**	80
12h, 2-Thienyl	B	**15h**	67
12i, Ferrocenyl	A	**15i**	87
12j, 3-Pyridyl	A	**15j**	70
12k, 2-Quinolyl	B	**15k**	69
12l, *c*-Hx	C	**15l**	62
12m, 2-Pyridyl	B	**15m**	50

a Method A: 1) H_5IO_6, $MeNH_2$, MeOH 2) acryloyl chloride, Na_2CO_3, acetone. Method B: 1) H_5IO_6, $MeNH_2$, MeOH 2) acryloyl chloride, triethylamine, DMAP (cat.). Method C: 1) lead tetraacetate, hydroxylamine hydrochloride 2) acryloyl chloride, Na_2CO_3, acetone. b Yield of pure product after column chromatography.

The unsaturated amides **13** were then subjected to the RCM reactions in order to prepare the six-membered α,β-unsaturated lactams **14** (Scheme) exploiting the commercially available ruthenium benzylidene complexes the so called 1st and 2nd generation Grubbs' catalysts **I** and **II**, respectively.



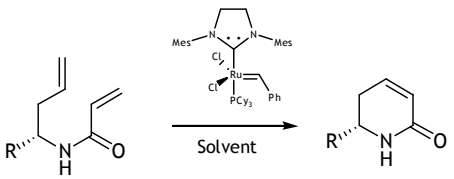
1st gen. Grubbs' catalyst



2nd gen. Grubbs' catalyst

Preliminary attempts carried out using **I** were not satisfactory, whereas **II** generally performed well, so the latter catalyst was chosen for the subsequent reactions. The results of the metathesis reactions performed on the unsaturated amides **13** are reported in the Table. In most cases good results were obtained by working with 5 mol% of catalyst in dichloromethane solution at the reflux temperature. Following the advancement of the reaction by t.l.c. or ^{1}H-NMR analysis the disappearance of the starting compound **13** was observed after 3h. After usual work-up, the expected products **14** were isolated in good yields after separation from minor amounts of by-products by medium pressure column chromatography. However, in the case of pyridyl containing substrates, the reaction did not work in the usual conditions. The 3-pyridyl derivative **13j** could be converted to the corresponding unsaturated lactam **14j** in 70% yield only in the presence of 2.5 equivalents of trifluoroacetic acid (TFA). However, for the 2-quinolyl and 2-pyridyl derivatives **13k** and **13m**, respectively, even the latter conditions did not allow for their satisfactory conversion. Surprisingly, the 2-quinolyl-substituted lactam **14k** was obtained in 40% yield by working in refluxing benzene in the absence of TFA. However, the 2-pyridyl-substituted lactam **14m** could not be obtained from **13m** working either in dichloromethane in the presence of TFA or HCl, or in benzene in the prescence of TFA.

It should be observed that the furyl-substituted lactam **14g** can be converted to the carboxy-substituted analogue **14** (R = CO_2H) and then the corresponding ester[13a] via routine oxidation of the furan ring.[22b] Similarly, Ni-Raney reduction/desulfurization of the thiophene ring[23] of **14h** would lead to the *n*-butyl-substituted lactam **14** (R = *n*-Bu); this route should be preferable to the alternative one starting from pentaneimines **9** or **11** (R = *n*-Bu), as linear aliphatic aldimines are less easily prepared than aromatic imines.

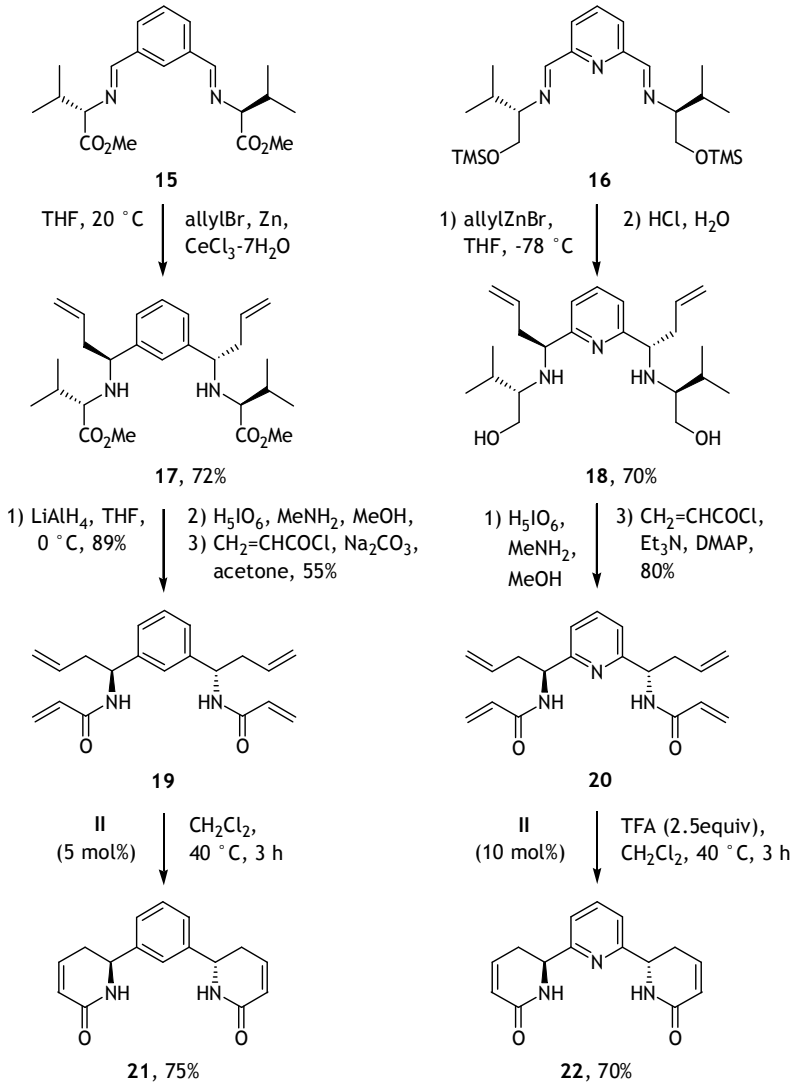


13 14

Acryloyl amides 13	II (mol%)	Solvent	Additive (equiv.)	Lactam	Yield (%)[b]
13a, Ph	5	DCM		**14a**	76
13b, 4-ClPh	5	DCM		**14b**	72
13c, 4-FPh	5	DCM		**14c**	77
13d, 4-MeOPh	5	DCM		**14d**	77c
13e, 3,4,5-$(MeO)_3$Ph	5	DCM		**14e**	69c
13f, 2-Naphthyl	5	DCM		**14f**	80c
13g, 2-Furyl	5	DCM		**14g**	60
13h, 2-Thienyl	5	DCM		**14h**	62
13i, Ferrocenyl	5	DCM		**14i**	78
13j, 3-Pyridyl	5	DCM		**14j**	0
13j, 3-Pyridyl	5	DCM	TFA (2.5)	**14j**	70
13k, 2-Quinolyl	5	DCM	TFA (2.5)	**14k**	0
13k, 2-Quinolyl	10	benzene		**14k**	40d
13l, *c*-Hx	5	DCM		**14l**	82
13m, 2-Pyridyl	5	DCM	TFA (2.5)	**14m**	0
13m, 2-Pyridyl	5	DCM	HCl (1)	**14m**	0
13m, 2-Pyridyl	10	benzene	TFA (2.5)	**14m**	0

a The reactions were carried out using the Grubbs' catalyst **II** for 3 h at the reflux temperature of the solvent. b Yield of product purified by column chromatography. c Using 2 mol% of the catalyst incomplete ring closure was observed after 3 h. d About 80% conversion of the starting diene was determined by 1H NMR analysis.

The synthetic sequence described for the preparation of aryl-substituted δ-lactams from mono-imines was then applied to the synthesis of the C_2-symmetric dilactams **21** and **22**, where the two rings are connected through a 1,3-disubstituted benzene ring or 2,6-disubstituted pyridine ring.

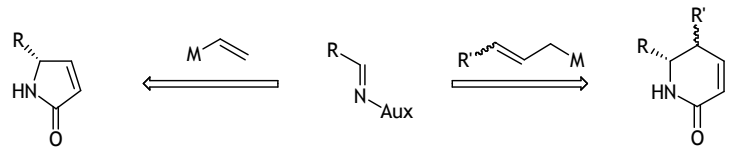


The diimine **15** derived from isophtalaldehyde and (*S*)-valine methyl ester was allylated by the Barbier protocol and gave the expected di-homoallylic amine **17** in good yield and with almost complete diastereoselectivity. Reduction of the ester groups to alcohol, oxidative cleavage and reaction of the primary amines with acryloyl chloride gave the unsaturated diamide **19**, then RCM gave the dilactam **21** in satisfactory overall yield. On the other hand, the imine **16** was prepared from (*S*)-valinol, followed by silylation of the hydroxyl groups. The Grignard protocol with allylzinc bromide at low temperature, gave the di-homoallylic amine **18** with d.r. 96:4 and the pure prevalent diastereomer was obtained in 70% yield after chromatography. Removal of the chiral auxiliaries and *N*,*N*'-diacroylation gave the unsaturated diamide **20** with a good overall yield. With our surprise, the double RCM reaction in the presence of TFA (2.5 equiv.) was successful for this compound using 10 mol% of catalyst, despite the failure previously observed for the mono-amide **13m**, as we obtained the dilactam **22** in a satisfactory yield.

4.3 Conclusions

The stereoselective synthesis of simple δ-substituted α,β̃unsaturated δ-lactams has been accomplished starting from readily available materials: aldehydes, optically pure primary amines, allyl halides or allylmetal compounds and acryloyl chloride, which were assembled by established methodologies allowing the easy and efficient formation of a carbon-nitrogen bond (imine formation) and three carbon-carbon bonds. In particular, the highly diastereoselective formation of the C5-C6 bond has been accomplished by two alternative protocols for the allylmetalation of chiral imines, which were obtained from (*S*)-valine methyl ester or (*S*)-valinol. Then, after removal of the *N*-substituent and *N*-acroylation of the primary homoallylic amine, the unsaturated lactam ring was built by a ring closing metathesis reaction.

As noted in the introduction a C5 substituent could be introduced diastereoselectively by using a γ-substituted allylmetal reagent, so forming two new stereocenters by combined auxiliary-induced and simple diastereoselectivities.



Moreover, the versatility of this route is further enhanced by the possibility to use the unsaturated lactams to construct more substituted/functionalized nitrogen heterocycles as the conjugated alkene and amide functions can undergo further transformations. For example, nucleophilic conjugate addition and reduction of the lactam carbonyl group can be sequentially used to prepare *cis*- and/or *trans*-2,4-disubstituted piperidines,[24] a structural motif that is present in a number of biologically and pharmacologically active compounds.[25]

Experimental section:

The following compounds have been previously described: **9a**, [9b] **9d**,[9b] **9h**,[21] **9k**,[22c] **10d**,[9b] **10h**,[21] **10j**,[9b] **12a**,[9b] **12g**,[22b] and **16**.[22d] The preparation of racemic lactams **13a**[26] and **14a**[16c] has been previously reported. The novel imines were prepared by the same procedures described previously.

Barbier Allylation of Imines 9: Zinc dust (1.31 g, 20 mmol) was added in small portions to a solution of the imine **9** (10 mmol), allyl bromide (1.8 g, 1.3 ml, 15 mmol) and CeCl3.7H2O (0.372 g, 1 mmol) in anhydrous THF (15 mL) at 0 °C, and the mixture was then stirred at room temperature. The reactions were monitored by TLC and GC/MS analyses and were usually complete within 1.5 h. To the mixture was added: saturated aqueous NH_4Cl (10 mL) and 40% NH_3 (10 ml), and the organic phase was extracted with Et_2O (2 x 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to give an oily residue, which was subjected to flash chromatography eluting with cyclohexane/ethyl acetate mixtures. Starting from the diimine **15**, two-fold amounts of reagents were required.

Reduction of Amino Esters 10 with $LiAlH_4$: A solution of the amino ester **10** (5 mmol) in anhydrous THF was added dropwise to a suspension of $LiAlH_4$ (0.380 g, 10 mmol) in THF (10 mL), cooled with an ice/NaCl bath. After 1 h, the reaction was quenched with 2.5 M NaOH (10 mL) (caution!, very exotermic) and then H_2O (10 ml), and the organic phase was extracted with Et_2O (2 x 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to give the products **12**, which were used as obtained in the successive step. Starting from the diamine **17**, two-fold amounts of reagents were required.

Organometallic Addition to the Imines 11 and 16: A solution of allyl bromide (1.3 mL, 1.8 g, 15 mmol,) in anhydrous THF (20 mL) was added dropwise to a stirred suspension of zinc dust (1.31 g, 20 mmol) in THF (8 mL). The reaction is exotermic and the rate of addition must be controlled to maintain the temperature below 50 °C. After the addition was complete, the mixture was stirred for 1 h, then stirring was stopped to allow the zinc dust to deposit on the bottom of the flask. The solution was taken with a syringe and transferred into an addition funnel, and finally added dropwise to a solution of the imine **11** (5 mL) in dry THF cooled at 78 °C. The reaction was monitored by TLC and GC-MS analyses and the *O*-trimethylsilyl amino alcohol was obtained by the usual work-up. The crude product was dissolved in Et_2O (5 mL) and treated with 1 M HCl (10 mL) for 1 h, then 2.5 M NaOH was added until pH 11 was reached and the organic material was extracted with Et_2O (2 x 10 ml). The combined ethereal layers were dried over Na_2SO_4, concentrated at reduced pressure and subjected to flash chromatography

eluting with cyclohexane/ethyl acetate mixtures. Starting from the diimine **16**, two-fold amounts of reagents were required.

Preparation of Propenamides from β-Amino Alcohols.

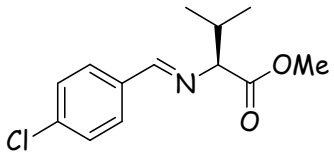
Procedure A: The amino alcohol **12a-j** (1 mmol) was dissolved in a mixture of MeOH (15 mL) and THF (5 mL), then 40% aq $MeNH_2$ (12 mL) was added. A solution of H_5IO_6 (0.800 g, 3.5 mmol) in H_2O (15 mL) was added dropwise while stirring. The reaction was slightly exothermic. The reaction is monitored by TLC and GC/MS analyses. When the reaction appeared complete (1-3 h), the mixture was concentrated at reduced pressure to remove most of the MeOH, and H_2O (15 ml) was added. The organic phase was extracted with Et_2O (2 x 20 mL) and the combined ethereal layers were dried over Na2SO4 and concentrated at reduced pressure. The residue was dissolved in acetone and Na2CO3 (0.372 g, 3 mmol) dissolved in 5 mL of H_2O was added. To the vigorously stirred mixture, at 0 °C, was added dropwise acryloyl chloride (0.18 g, 163 □L, 2 mmol) dissolved in acetone (10 mL). The reaction was monitored by TLC and GC/MS analyses, and when it appeared complete (ca 2 h) most of the solvent was evaporated at reduced pressure, H_2O (15 mL) was added and the organic phase was extracted with Et_2O (2 x 15 mL). The combined ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure and the residue was subjected to flash-chromatography to give the pure amide **13a-j**. Compound **19** was similarly obtained from **17** by using two-fold amounts of reagents.

Procedure B: Cleavage of the *N*-substituent of **12k**,**m** was conducted as described above, then the crude primary amine was dissolved in THF (10 mL), and triethylamine (0.15 g, 0.21 mL) and DMAP (0.01 g) were added. To the vigorously stirred mixture at 0 °C was added dropwise acryloyl chloride (0.13 g, 0.12 mL, 1.5 mmol) dissolved in THF (10 mL) and a white precipitate formed immediately. The reaction was monitored by TLC and GC/MS analyses. The solvent was removed at reduced pressure and the crude product was subjected to flash-cromatography to give the pure amide **13k**,**m**. Compound **20** was similarly obtained from **18** by using the proper amounts of reagents.

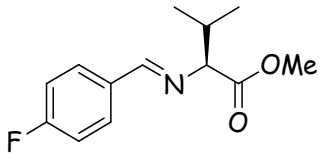
Procedure C: The amino alcohol **12l** (0.63 mmol) was dissolved in a 1:1 MeOH/DCM mixture (6 mL), then lead tetraacetate (0.332 g, 0.75 mmol) was added to the stirred solution cooled to 0 °C. When TLC analysis showed complete consumption of the starting material, hydroxylamine hydrochloride (0.040 g, 6.3 mmol) was added and the mixture was vigorously stirred for 3 h. H_2O (5 mL) was added and the insoluble material was filtered off, then the organic phase was extracted with Et_2O (2 x 10 mL). The combined

ethereal layers were dried over Na_2SO_4 and concentrated at reduced pressure to yield the crude primary amine, which was converted into the amide **13l** as described in procedure A.

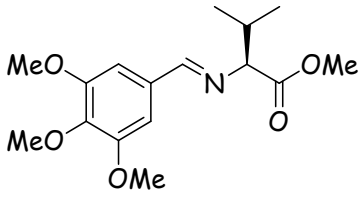
Preparation of α,β-Unsaturated δ-Lactams: The unsaturated amide (1 mmol) was dissolved in anhydrous DCM or C_6H_6 (5 mL) and TFA (0.29 g, 192 μL, 2.5 mmol) was added for compounds **13j**,**k** and **20**. The solution was de-aerated by bubbling a stream of Ar through it, the Ru-complex **II** (0.042 g, 0.05 mmol) was added, the solution was again de-aerated and heated to reflux. The progress of the reaction was monitored by TLC analysis and the disappearance of the starting material was observed within 3 h. The solvent was removed at reduced pressure and the residue was subjected to flash-chromatography.



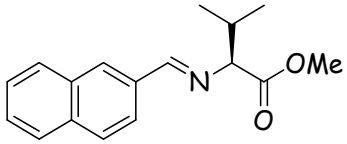
Methyl N-(4-chlorobenzylidene) (*S*)-valinate (9b): White solid; m.p. 52 °C; $[\alpha]_D^{20}$ +101.6 (c 0.9, $CHCl_3$); IR (KBr) *v* = 2957.0, 1736, 1644, 1488, 1386, 1194, 833. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.21 (s, 1 H), , 7.73 (d, *J* = 8.1, 2 H), 7.39 (dd, *J* = 8.1 Hz, 2 H), 3.75 (s, 3 H), 3.67 (d, *J* = 7.4 Hz, 1 H), 2.38 (sept, *J* = 6.9 Hz, 1 H), 0.93 (d, 3 H, *J* = 6.9 Hz, 3 H), 0.96 (d, 3 H, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 161.9, 137.1, 134.1, 129.7, 128.8, 80.2, 52.0, 31.7, 19.5, 18.6. (EI) m/z = 194 (100), 196 (35), 210 (20), 89 (19), 152 (12), 252 (1, M^+). Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found C, 61.41; H, 6.38; N, 5.50.



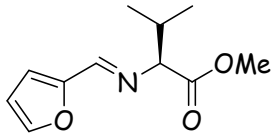
Methyl N-(4-fluorobenzylidene) (*S*)-valinate (9c): colourless oil; $[\alpha]_D^{20}$ -107.4 (1.8, $CHCl_3$); IR (neat): *v* = 2962, 1740, 1644, 1602, 1509, 1231; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.14 (s, 1 H), 7.71 (dd, *J* = 5.6 Hz *J* = 8.4 Hz, 2 H), 7.01 (dd, *J* = 8.4 Hz, *J* = 6.9 Hz, 2 H), 3.67 (s, 3 H), 3.62 (d, *J* = 7.2 Hz, 1 H), 2.32 (sept, *J* = 6.8 Hz, 1 H), 0.89 (d, 3 H, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 164.5 (d, *J* = 251.4 Hz), 161.6, 131.9, 130.4 (d, *J* = 8.6 Hz), 115.5 (d, *J* = 21.9 Hz), 80.0, 51.78, 31.6, 19.3, 18.5. MS (EI) *m/z* = 178 (100), 135 (25), 108 (24), 55 (20), 194 (21), 238 (1, M^+ 1).



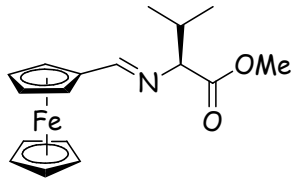
Methyl N-(3,4,5-trimethoxybenzylidene) (*S*)-valinate (9e): colourless oil, $[\alpha]_D^{20}$ -87.8 (c 1.3, $CHCl_3$); IR (neat): *v* = 3075.3, 2941, 1728, 1641, 1127.; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.15 (s, 1 H), 7.03 (s, 2 H), 3.91 (s, 6 H), 3.88 (s, 3 H), 3.75 (s, 3 H), 3.63 (d, *J* = 7.6 Hz, 1 H), 2.37 (sept, *J* = 6.8 Hz, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 162.8, 153.4, 133.6, 131.2, 105.6, 80.3, 60.9, 56.3, 51.9, 51.8, 31.7, 19.5, 18.7. MS (EI) *m/z* = 250 (100), 309 (M^+, 50), 206 (44), 192 (21), 294 (8).



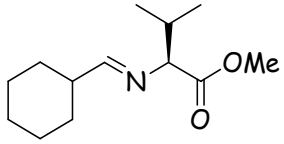
Methyl N-(2-naphthylidene) (*S*)valinate (9f): pale yellow solid m.p. 122-123 °C; $[\alpha]_D^{20}$ –120.5 (c 0.8, $CHCl_3$). IR (KBr): *v* = 3051.1, 2951.5, 2869.8, 1733.8, 1635.2, 1434.4, 1350.2, 1161.9, 972.9 , ^{1}H NMR (200 MHz, $CDCl_3$): δ= 8.41 (s, 1 H), 8.10 (m, 2 H), 7.89 (m, 3 H), 7.51 (m, 2 H), 3.78 (s, 3 H), 3.74 (d, *J* = 7.0 Hz, 1 H), 2.42 (sept, *J* = 6.8 Hz, 1 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.4, 163.3, 134.8, 133.3, 132.9, 130.4, 128.6, 128.4, 127.8, 127.3, 126.4, 124.1, 80.5, 51.9, 31.8, 19.5, 18.7. MS (EI) m/z = : 210 (100), 167 (38), 139 (29), 226 (21), 269 (13, M^+). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found C, 76.00, H, 7.13, N, 5.18.



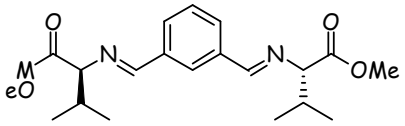
Methyl *N*-(2-furylidene) (*S*)-valinate (9g): pale yellow oil; $[\alpha]_D^{20}$ -106.2 (c 1.1, $CHCl_3$); IR (neat) *v* =3122, 2961, 1740, 1645, 1482, 1262, 1198, 1018. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 7.56 (d, *J* = 1,7 Hz, 1 H), 6.86 (d, *J* = 3.4 Hz, 1 H), 6.51 (dd, *J* = 3.4 Hz, *J* = 1.7 Hz, 1 H), 3.76 (s, 3 H), 3.60 (d, *J* = 7.7 Hz, 1 H), 2.41 (sept, *J* = 6.8 Hz), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H). ^{13}CNMR (75 MHz, $CDCl_3$): δ = 171.9, 151.4, 150.8, 144.9, 115.0, 111.5, 80.4, 51.7, 31.4, 19.2, 18.5. MS (EI) *m/z* = 150 (100), 166 (38), 111 (24), 55 (21), 80 (17), 209 (M+, 1).



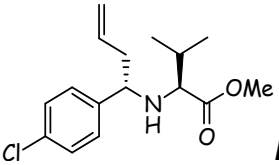
Methyl *N*-ferrocenylidene (*S*)-valinate (9i): Red solid, m.p. 88-88.5 °C; $[\alpha]_D^{20}$ -2.7 (c 0.37, $CHCl_3$); IR (KBr): *v* = 2923, 2853, 1736, 1691, 1635, 1461, 1376. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 4.69 (m, 2 H), 4.38 (d, *J* = 1.9 Hz, 1 H), 4.36 (d, *J* = 1.9 Hz, 1 H), 4.17 (s, 5 H), 3.72 (s, 3 H), 3.48 (d, *J* = 7.9 Hz, 1 H), 2.33 (dsept, *J* = 7.9 Hz, *J* = 6.7 Hz, 1 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 163.5, 80.9, 79.8, 70.6, 69.5, 69.1, 68.9, 68.4, 51.8, 30.9, 19.5, 18.7. Anal. Calcd for $C_{17}H_{21}FeNO_2$: C, 62.40; H, 6.47; Fe, 17.07; N, 4.28. Found C, 62.24; H, 6.50; Fe, 17.02; N, 4.26.



Methyl N-cyclohexylidene (*S*)-valinate (9l) colourless oil, $[\alpha]_D^{20}$ -62.8 (c 1.6, $CHCl_3$). IR (neat): *v* = 2927, 2853, 1739, 1664, 1449, 1196. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 5.8 Hz, 1 H), 3.73 (s, 3 H), 3.36 (d, *J* = 7.4 Hz, 1 H), 2.23 (sept, *J* = 6.8 Hz, 1 H), 1.78 (m, 6 H), 1.28 (m, 5 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 171.7, 80.2, 51.6, 43.4, 31.1, 29.7, 29.4, 25.7, 25.1, 19.2, 19.0, 18.2. (EI) m/z: 166 (100), 95 (70), 72 (54), 157 (61), 182 (44), 225 (M+, 5). MS (EI) *m/z* = 166 (100), 95 (70), 157 (61), 72 (57), 182 (44), 225 (M^+, 5).

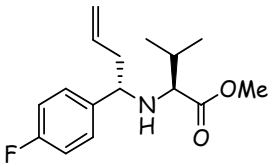


(15): Yellowish oil; $[\alpha]_D^{20}$ -134.6 (c 0.58, $CHCl_3$). IR (neat): *v* = 2962, 2872, 1740, 1643, 1468, 1198, 1027. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.27 (s, 2 H), 7.03 (s, 1 H), 8.01 (s, 1 H), 8.01 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 2 H), 8.01 (t, *J* = 7.7 Hz, 1 H), 3.73 (s, 6 H), 3.63 (d, *J* = 7.4, Hz, 2 H), 2.37 (sept, *J* = 6.9 Hz, 2 H), 0.96 (d, *J* = 6.9 Hz, 6 H), 0.92 (d, *J* = 6.9 Hz, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.2, 162.6, 136.1, 130.7, 128.9, 128.8, 80.2, 51.9, 31.6, 19.4, 18.6. MS (EI) *m/z* = 301 (100), 171 (15), 55 (10), 194 (21), 360 (M^+, 4).

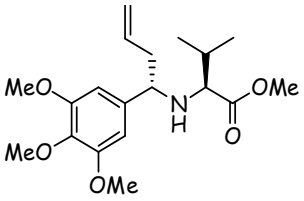


Methyl *N*-[1(*S*)-(4-chlorophenyl)-3-buten-1-yl] (*S*)-valinate (10b): colourless oil; $[\alpha]_D^{20}$ -118.4 (c 1.1, $CHCl_3$). IR (neat): *v* = 3077.9, 2961.6, 1732.3, 1640.5, 1469.6, 1155.4, 994.1 . ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 5 H), 5.71 (m, 1 H), 5.12

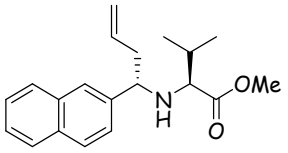
(m, 2 H), 3.71 (s, 3 H), 3.47 (dd, *J* = 8.12 Hz, *J* = 5.5 Hz, 1 H), 2.72 (d, *J* = 6.1 Hz, 1 H), 2.20-2.45 (m, 2 H), 2.00 (bs, 1 H), 1.81 (sept , *J* = 6.9 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 142.1, 134.8, 134.8, 132.6, 128.6, 128.4 117.7 , 64.3, 60.1, 51.3, 43.8, 31.6, 19.4, 18.4. MS (EI) *m/z* = 254 (100), 194 (58), 72 (48), 165 (42), 125 (40) 55 (31). Anal. Calcd for $C_{16}H_{22}ClNO_2$: C, 64.97; H, 7.50; N, 4.74. Found C, 64.87; H, 7.53; N, 4.68.



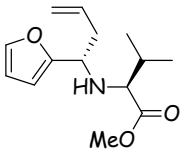
Methyl *N*-[1(*S*)-(4-fluorophenyl)-3-buten-1-yl] (*S*)-valinate (10c): colourless oil; $[\alpha]_D^{20\sim}$ -100.4 (c 0.96, $CHCl_3$). IR (neat): *v* = 3077.1, 2962.0, 1735.2, 1604.4, 1509.0, 1222.0; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 5.5 Hz, *J* = 8.6 Hz, 2 H), 6.90 (dd, *J* = 8.6 Hz, *J* = 8.6 Hz, 2 H), 5.74 (m, 2 H), 3.69 (s, 3 H), 3.49 (dd, *J* = 5.6 Hz, *J* = 7.6 Hz, 1 H), 2.73 (d, *J* = 6.2 Hz, 1 H), 2.20-2.45 (m, 2 H), 2.01 (bs, 1 H), 1.81 (m, , 1 H), 0.89 (d, 3 H, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.8, 161.9 (d, *J* = 240 Hz), 139.1 (d, *J* = 2.2 Hz), 134.9, 128.8 (d, *J* = 7.6 Hz), 117.7, 114.9 (d, *J* = 22.2 Hz), 64.2, 59.9, 51.1, 43.8 31.5, 19.3, 18.3. MS (EI) *m/z* = 238 (100), 178 (68), 149 (57), 109 (45), 72 (20). Anal. Calcd for $C_{16}H_{22}FNO_2$: C, 68.79; H, 7.94; F, 6.80; N, 5.01. Found C, 68.72; H, 7.98; N, 4.99.



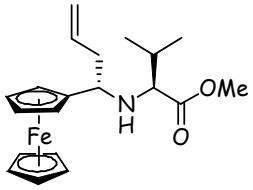
Methyl *N*-[1(*S*)-(3,4,5-trimethoxyphenyl)-3-buten-1-yl] (*S*)-valinate (10e): colourless oil; $[\alpha]_D^{20\sim}$ -101.3 (c 0.9, $CHCl_3$). IR (neat): *v* = 2960, 1737 1585, 1127. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.52 (s, 2 H), 5.70 (m, 1 H), 5.08 (m, 2 H), 3.77 (s, 6 H), 3.75 (s, 3 H), 3.64 (s, 3 H), 3.37 (dd, *J* = 8.6 Hz, *J* = 4.4 Hz, 1 H), 2.77 (d, *J* = 5.7 Hz), 2.25-2.45 (m, 2 H), 1.95 (bs, 1 H), 1.77 (sept, *J* = 7.2 Hz, 1 H), 0.89 (d, *J* = 7.2 Hz, 3 H), 0.85 (d, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 152.9, 134.8, 139.3, 135.0, 117.5, 103.8, 64.0, 60.1, 55.7, 51.0, 43.5, 19.4, 31.5, 19.5, 18.2. MS (EI) *m/z* = 310 (100), 250 (25), 221 (16),190 (11), 55 (10), 211 (4). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99; O, 22.76. Found C, 64.86; H, 8.35; N, 3.97.



Methyl *N*-[1(*S*)-(2-naphthyl)-3-buten-1-yl] (*S*)-valinate (10f): colourless oil, $[\alpha]_D^{20}$ -140.6 (c 0.65, $CHCl_3$). IR (neat): *v* = 3056, 2969, 1733, 1639, 1601, 1154, 917. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00-7.65 (m, 4 H), 7.6-7.25 (m, 3 H), 5.80 (m, 1 H), 5.13 (m, 2 H), 3.74 (s, 3 H) 3.70 (dd, *J* = 8.1 Hz, *J* = 5.7 Hz, 1 H), 2.83 (d, *J* = 6.2 Hz, 1 H), 2.40-2.60 (m, 2 H), 2.12 (bs, 1 H), 1.77 (sept , *J* = 6.8 Hz, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.00, 141.0, 135.1, 133.3, 132.9, 127.9, 127.7, 127.6, 126.5, 125.8, 125.5, 125.4, 64.3, 60.8, 51.2, 43.6, 31.7, 19.4, 18.4. MS (EI) *m/z* = 270 (100), 181 (50), 210 (40), 164 (30), 141 (20). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50; O, 10.28. Found C, 77.00; H, 8.11; N, 4.47.

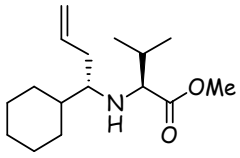


Methyl *N*-[1(*S*)-(2-furyl)-3-buten-1-yl] (*S*)-valinate (10g): colourless oil; $[\alpha]_D^{20}$ -69.5 (c 1.7, $CHCl_3$); IR (neat): *v* = 3332, 3076, 2961, 2925, 1735, 1604, 1509, 1221, 1200, 1154, 836. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 1.8 Hz, *J* = 0.9 Hz, 1 H), 6.28 (dd, *J* = 3.1 Hz, *J* = 1.8 Hz, 1 H), 6.15 (dd, *J* = 3.1 Hz, *J* = 0.9 Hz, 1 H), 5.73 (m, 1 H), 5.13 (d, *J* = 16.7 Hz, *J* = 1.6 Hz, 1 H), 5.08 (d, *J* = 9.1 Hz, *J* = 1.6 Hz, 1 H), 3.7 (s, 3 H), 3.65 (dd, *J* = 7.8 Hz, *J* = 6.0 Hz, 1 H), 2.97 (d, *J* = 5.6 Hz, 1 H), 2.53 (ddd, *J* = 13.9 Hz, *J* = 6.0 Hz, *J* = 1.4 Hz, 1 H), 2.43 (ddd, *J* = 13.9 Hz, *J* = 7.8 Hz, *J* = 0.9 Hz, 1 H), 1.92 (sept, *J* = 6.8 Hz ,1 H) 0.88 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 183.0, 163.0, 175.6, 156.2, 141.6, 134.7, 117.8, 109.9, 106.6, 64.4, 54.6, 51.4, 40.1, 31.7, 19.2, 18.4. MS (EI) *m*/z = 96 (100), 55 (73), 150 (62), 151 (8), 162 (2), 191 (M^+, 2). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found C, 66.97; H, 8.45; N, 5.49.

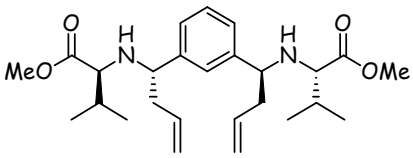


Methyl *N*-[1(*S*)-(ferrocenyl)-3-buten-1-yl] (*S*)-valinate (10i): red crystals; m.p. = 84-84.5 °C; $[\alpha]_D^{20}$ -34.0 (c 0.4, $CHCl_3$). IR (KBr): *v* = 3074, 2962, 1736, 1643, 1445, 1317, 1153, 989, 812.; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.17 (m, 2 H), 4.14 (s, 5 H), 4.13 (m, 4 H), 3.72 (s, 3 H), 3.36 (dd, *J* = 3.5 Hz, *J* = 9.6 Hz 1 H), 3.31 (d, *J* = 6.0 Hz), 2.27 (ddd, *J* = 14.2 Hz, *J* = 3.5 Hz, *J* = 1.8 Hz ,1 H), 2.35 (ddd, *J* =

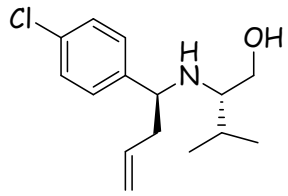
14.2 Hz, *J* = 9.6 Hz, *J* = 9.1 Hz ,1 H), 1.6 (bs, 1 H), 0.89 (d, 3H, *J* = 6.8 Hz, 3 H), 1.83 (sept, , *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, 3,H, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.5, 136.1, 117.3, 91.5, 68.5, 68.3, 67.5, 66.6, 65.9, 63.9, 54.4, 51.2, 41.7, 31.8, 18.8, 18.5. Anal. Calcd for $C_{20}H_{27}FeNO_2$: C, 65.05; H, 7.37; Fe, 15.12; N, 3.79. Found C, 64.45; H,7.40; Fe, 15.10; N, 3.74.



Methyl *N*-[1(*S*)-cyclohexyl-3-buten-1-yl] (*S*)-valinate (10*l*): colourless oil, $[\alpha]_D^{20}$ -18.1 (c 1.3, $CHCl_3$). IR (neat): *v* = 2929, 1735, 1640, 1592, 1420, 1129, 1012. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.73 (m, 1 H), 5.08 (m, 2 H), 3.70 (s, 3 H), 3.02 (d, *J* = 6.6 Hz, 1 H), 2.22 (m, 2 H), 2.1-1.0 (m, 2 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.7, 116.6, 61.4, 60.4, 59.6, 40.8, 36.0, 29.2, 29.1, 28.7, 26.7, 26.6, 19.6, 18.1. MS (EI) *m/z* = 226 (100), 184 (49), 72 (36), 95 (35), 166 (33), 208 (22), 266 (M^+, 1). Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.86; H, 10.93; N, 5.24. Found C, 71.80; H, 10.89; N, 5.20.

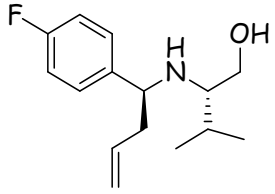


(17): colourless oil; $[\alpha]_D^{20}$ -138.2 (c 0.9, $CHCl_3$). IR (neat): *v* = 3076, 2960.8, 1735, 1640, 1468, 1434, 1198, 994. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 4 H), 5.10 (m, 2 H), 5.08 (m, 2 H), 3.70 (s, 6 H), 3.49 (dd, *J* = 8.1 Hz, *J* = 5.7 Hz, 1 H), 2.78 (d, *J* = 6.1 Hz, 2 H), 2.25-2.45 (m, 2 H), 2.09 (bs, 1 H), 1.77 (sept , *J* = 6.7 Hz, 1 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 143.5, 135.3, 127.9, 126.6, 117.4, 62.2, 60.8, 51.2, 43.8, 31.7, 19.5, 18.4. MS (EI) *m/z* = 403 (100), 55 (67), 141 (52),272 (40), 247 (26), 385 (18). Anal. Calcd for $C_{26}H_{40}N_2O_4$: C, 70.24; H, 9.07; N, 6.30. Found C, 70.28; H, 9.09; N, 6.24.

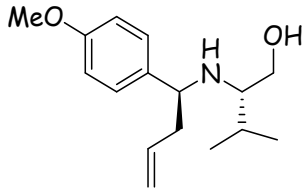


***N*-[1(*S*)-(4-Chlorophenyl)-3-buten-1-yl] (*S*)-valinol (12b)**: colourless oil; $[\alpha]_D^{20}$ -35.5 (c 1.2, $CHCl_3$). IR (neat): *v* = 3423, 3017, 2958, 1640, 1490, 1086, 917. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.48 Hz, 2 H), 7.21 (d, *J* = 8.48 Hz, 2 H), 5.71 (m, 1 H), 5.05 (m, 2 H) 3.77 (m, 1 H) 3.62 (dd, *J* = 10.8 Hz, *J* = 4.12 Hz, 1 H), 3.41 (dd, *J* = 10.8 Hz, *J* = 4.53 Hz ,1 H), 2.42 (m, 2 H), 2.22 (ddd, *J* = 6.6 Hz, *J* = 4.12

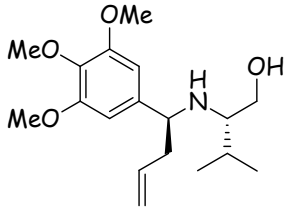
Hz, *J* = 4.53 Hz 1 H), 1.71 (sept , *J* = 6.8 Hz, 1 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H). ^{13} CNMR (50 MHz, $CDCl_3$): δ = 142.5, 134.8, 132.6, 128.4, 61.1, 59.9, 59.4, 42.7, 29.28, 19.3, 18.9. Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 67.28; H, 8.28; N, 5.23. Found C, 67.22; H, 8.31; N, 5.20.



***N*-[1(*S*)-(4-Fluorophenyl)-3-buten-1-yl] (*S*)-valinol (12c)**: colourless oil; $[\alpha]_D^{20}$ -34.2 (c 0.83, $CHCl_3$). IR (neat) *v* = 3417, 3076, 2957, 1640, 1604, 1509, 1221, 1048. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24(m, 2 H), 7.02 (m, 2 H), 5.66 (m, 1 H), 5.02 (m, 2 H), 3.73 (t, *J* = 8.1 Hz, 1 H), 3.61 (dd, *J* = 10.8 Hz, *J* = 4.1 Hz, 1 H), 3.40 (dd, *J* = 10.8 Hz, *J* = 4.5 Hz, 1 H), 2.40 (m, 2 H), 1.67 (sept, *J* = 6.9 Hz, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 128.5 (d, *J* = 8.1 Hz), 117.5, 115.2 (d, *J* = 21.2 Hz), 61.1, 60.04, 59.4, 42.8, 29.4, 19.4, 18.9. Anal. Calcd for $C_{15}H_{22}FNO$: C, 71.68; H, 8.82; N, 5.57. Found C, 71.56; H, 8.85; N, 6.34.

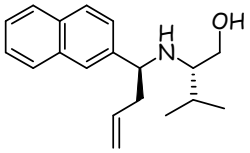


***N*-[1(*S*)-(4-Methoxyphenyl)-3-buten-1-yl] (*S*)-valinol (12d)**: colourless oil; $[\alpha]_D^{20}$ -24.8 (c 0.8, $CHCl_3$). IR (neat): *v* = 3416, 2958, 1611, 1585, 1512, 1246, 1037. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.2 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H) 5.68 (m, 1 H), 5.15 (d, *J* = 10.6 Hz, *J* = 1.3 Hz, 1 H), 5.05 (d, *J* = 8.6 Hz, *J* = 1.3 Hz, 1 H), 3.83 (s, 6 H), 3.71 (dd, *J* = 17.6 Hz, *J* = 8.6 Hz, 1 H), 3.62 (dd, *J* = 10.6 Hz, *J* = 4.4 Hz, 1 H), 3.37 (dd, *J* = 10.6 Hz, *J* = 4.0 Hz, 1 H), 2.36 (m, 2 H), 2.27 (dd, *J* = 4.4 Hz, *J* = 4.0 Hz, 1 H), 1.71 (sept , *J* = 6.8 Hz, 1 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.9, 136.0, 127.9, 117.1, 113.7, 61.0, 59.9, 59.4, 55.2, 42.7, 41.1, 29.4, 19.4, 18.9. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found C, 72.99; H, 8.59; N, 5.28.

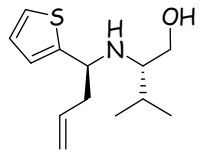


***N*-[1(*S*)-(3,4,5-Trimethoxyphenyl)-3-buten-1-yl] (*S*)-valinol (12e):** colourless oil; $[\alpha]_D^{20}$ –29.6 (c 0.88, $CHCl_3$). IR (neat): *v* = 3439, 2955, 1639,1592, 1436,

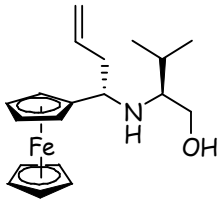
1325, 1232, 1009. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.48 (s, 2 H), 5.72 (m, 1 H), 5.05 (m, 2 H) 3.83(s, 6 H), 3.82 (s, 3 H), 3.71 (dd, *J* = 6.4 Hz, *J* = 6.2 Hz, 1 H) 3.60 (dd, *J* = 10.7 Hz, *J* = 4.31 Hz, 1 H), 3.40 (dd, *J* = 10.7 Hz, *J* = 4.22 Hz, 1 H), 2.36 (dd, *J* = 6.7 Hz, *J* = 6.6 Hz, 1 H), 2.12 (m, 1 H), 1.68 (sept , *J* = 6.8 Hz, 1 H), 0.89 (d, 3 H, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0, 139.9, 136.7, 135.3, 117.3, 103.7, 60.9, 60.7, 60.1, 59.8, 56.0, 42.9, 29.3, 19.4, 19.0. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found C, 66.88; H, 9.02; N, 4.35.



***N*-[1(*S*)-(2-Naphthyl)-3-buten-1-yl] (*S*)-valinol (12f)**: colourless oil; $[\alpha]_D^{20}$ -34.8 (c 0.95, $CHCl_3$). IR (neat): *v* = 3396, 3056, 2957, 1639, 1507, 1466, 1048. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 3 H), 7.70 (s, 1 H), 7.5 (m, 3 H), 5.75 (m, 1 H), 5.08 (m, 2 H), 3.92 (dd, *J* = 6.7 Hz, *J* = 6.9 Hz, 1 H), 3.69 (dd, *J* = 10.8 Hz, *J* = 4.1 Hz, 1 H), 3.69 (dd, *J* = 10.8 Hz, *J* = 4.5 Hz, 1 H), 2.55 (m, 2 H), 2.30 (ddd, *J* = 6.6 Hz, *J* = 4.13, *J* = 4.42 Hz 1 H), 1.74 (sept, *J* = 6.7 Hz, 1 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 135.2, 133.2, 132.8, 128.2, 127.7, 127.6, 126.1, 126.0, 126.6, 124.7, 117.3, 61.0, 60.1, 59.8, 42.6, 29.3, 19.5, 18.9. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94; O, 5.65. Found C, 8.41; H, 8.93; N, 4.90.

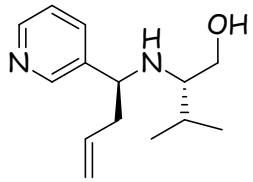


***N*-[1(*S*)-(2-Thienyl)-3-buten-1-yl] (*S*)-valinol (12h)**: colourless oil; $[\alpha]_D^{20}$ -37.2 (c 1.1, $CHCl_3$) IR (neat): *v* = 3390, 3075, 2957, 1641, 1464, 1039, 918. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (m,1 H), 6.92 (m, 2 H), 5.76 (m, 1 H), 5.11 (m, 2 H), 4.06 (t, *J* = 6.9 Hz, 1 H), 3.61 (dd, *J* = 10.9 Hz, *J* = 4.1 Hz, 1 H), 3.45 (dd, *J* = 10.9 Hz, *J* = 4.3 Hz, 1 H), 2.54 (m, 2 H), 1.73 (sept, *J* = 7.0 Hz, 1 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.86 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6, 134.8, 126.1, 124.1, 123.7, 117.5, 61.0, 59.9, 55.5, 43.3, 26.3, 16.3, 18.8. Anal. Calcd for $C_{13}H_{21}NOS$: 65.23; H, 8.84; N, 5.85; S, 13.40. Found C, 65.17; H, 8.81; N, 5.81; S, 13.36.

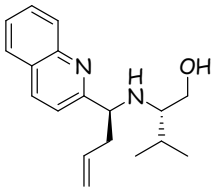


***N*-[1(*S*)-(Ferrocenyl)-3-buten-1-yl] (*S*)-valinol (12i)**: red oil; $[\alpha]_D^{20}$ +37.0 (c 0.58, $CHCl_3$). IR (neat): *v* = 3482, 3093, 2957, 1639, 1437, 1106. ^{1}H NMR (200 MHz,

$CDCl_3$): δ = 5.86 (m, 1 H,), 5.09 (m, 2 H), 4.16 (s, 5 H), 4.11 (m, 4 H), 3.57 (dd, *J* = 10.5 Hz, *J* = 4.8 Hz, 1 H), 3.57 (dd, *J* = 10.5 Hz, *J* = 6.3 Hz, 1 H), 3.49 (dd, *J* = 7.1 Hz, *J* = 5.3 Hz, 1 H), 3.33 (dd, *J* = 10.5 Hz, *J* = 8.5 Hz, 1 H), 2.56 (m, 1 H), 2.40 (m, 2 H), 1.80 (sept, 1 H, *J* = 6.8 Hz, 1 H), 0.91 (d, *J* = 6.8 Hz, 1 H), 0.91 (d, *J* = 6.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.0, 116.8, 92.8, 68.3, 67.4, 67.0, 66.8, 66.0, 61.0, 60.3, 54.2, 41,0, 29.4, 19.9, 18.1. Anal. Calcd for $C_{21}H_{32}FeNO$: C, 68.11; H, 8.71; Fe, 15.08; N, 3.78. Found C, 68.02; H, 8.73; Fe, 15.05; N, 3.76.

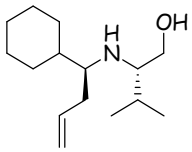


(*S*)-2-[(*S*)-1-(3-pyridyl)-3-butenylamino]-3-methyl-1-butanol (12j): yellowish oil; $[\alpha]_D^{20}$ -58.8 (c 2.0, $CHCl_3$). IR (neat): *v* = 3373, 3078, 2957, 2926, 2872, 1640, 1593, 1579, 1467, 1429, 1384, 1029, 918, 809, 716. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.46 (m, 2 H), 7.02 (m, 2 H), 7.67 (dt, *J* = 2.0 Hz, *J* = 7.9 Hz, 1 H), 7.26 (ddd, *J* = 0.8 Hz, *J* = 4.7 Hz, *J* = 7.8 Hz, 1 H), 5.67 (m, 1 H), 5.04 (m, 2 H), 3.82 (t, *J* = 6.9 Hz, 1 H), 3.64 (dd, *J* = 4.3 Hz, *J* = 11.0 Hz, 1 H), 3.47 (dd, *J* = 4.6 Hz, *J* = 11.0 Hz, 1 H), 2.41 (m, 2 H), 2.17 (dd, *J* = 4.3 Hz, *J* = 4.6 Hz, 1 H),1.68 (sept, *J* = 6.9 Hz, 1 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 148.4, 139.5, 134.8, 134.4, 123.4, 118.0, 61.2, 60.1, 57.5, 42.7, 29.2, 19.1, 18.9. GC-MS (EI) m/z = 193 (100), 132 (78), 107 (75), 130 (48), 117 (39), 203 (38), 92 (21). Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found C, 71.50; H, 9.49; N, 11.91.

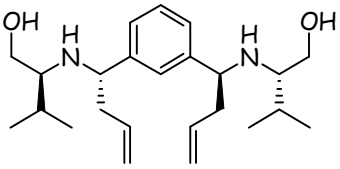


***N*-[1(*S*)-(2-Quinolyl)-3-buten-1-yl] (*S*)-valinol**: **(12k)**: yellow oil $[\alpha]_D^{20}$ -52.2 (c 0.25, $CHCl_3$). IR (neat): *v* = 3313, 2960, 1640, 1599, 1082, 837. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.2 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.83 (ddd, *J* = 8.6 Hz, *J* = 6.9 Hz, *J* = 1.5 Hz, 1 H), 7.54 (ddd, *J* = 8.1 Hz, *J* = 6.9 Hz, *J* = 1.1 Hz, 1 H), 7.44 (d, *J* = 8.6 Hz, 1 H), 5.86 (m, 1 H), 5.11 (m, 2 H), 4.08 (dd, *J* = 7.3 Hz, *J* = 5.9 Hz, 1 H), 3.71 (dd, *J* = 10.9 Hz, *J* = 4.1 Hz), 3.47 (dd, *J* = 10.9 Hz, *J* = 4.8 Hz), 2.61 (m, 2 H), 2.28 (ddd, *J* = 6.3 Hz, *J* = 4.8 Hz, *J* = 4.4 Hz ,1 H), 1.72 (sept, *J* = 6.9 Hz, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 147.5, 136.2, 135.1, 129.4, 128.9, 127.5, 127.3, 126.0, 120.1, 117.7, 62.8, 61.6,

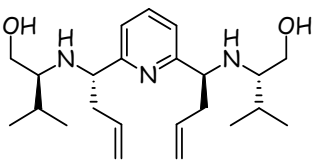
60.2, 42.1, 29.3, 19.5, 18.8. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found C, 76.08; H, 8.54; N, 9.81.



***N*-[1(*S*)-Cyclohexyl-3-buten-1-yl] (*S*)-valinol (12*l*)**: colourless oil; $[\alpha]_D^{20}$ +25.5 (c 0.73, $CHCl_3$). IR (neat): *v* = 3405, 2924, 1639, 1449, 1053. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.06 (m, 2 H), 3.52 (dd, *J* = 10.6 Hz, *J* = 4.2 Hz, 1 H), 3.29 (dd, *J* = 10.8 Hz *J* = 6.3 H, 1 H), 2.1 (m, 1 H) 2.05 (m, 1 H), 1.9-1.1 (m, 12 H) ,0.95 (d, *J* = 7.0 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H). ^{13}CNMR (50 MHz, $CDCl_3$): δ = 136.7, 116.6, 61.4, 60.4, 59.6, 40.7, 36.0, 29.2, 29.1, 28.7, 26.7, 26.6, 16.6, 18.1. MS (EI) *m*/*z* 198 (100), 55 (60), 95 (50), 67 (49), 156 (48), 180 (32), 208 (29), 238 ($M^{+\tilde{}}$ 1, 2). Anal. Calcd for $C_{15}H_{29}NO$: C, 75.26; H, 12.21; N, 5.85. Found C, 74.06; H, 12.23; N, 5.83.

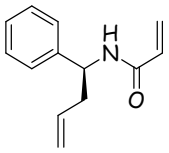


1,3-Di[(1*S*)-(1)-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]amino-3-buten-1-yl]benzene: by reduction of **17** with $LiAlH_4$; colourless oil; $[\alpha]_D^{20\tilde{}}$ -25.8 (c 0.31, $CHCl_3$). IR (neat): *v* = 3384, 3076, 2926, 1639.8, 1465, 1046. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 (m, 4 H), 5.68 (m, 2 H), 5.04 (m, H), 3.71 (dd, *J* = 6.9 Hz, *J* = 6.9 Hz, 2 H), 3.61 (dd, *J* = 11.1 Hz, *J* = 4.1 Hz, 2 H), 3.37 (dd, *J* = 11.4 Hz. *J* = 4.1 Hz, 2 H), 2.78 (bs, 2 H), 2.46 (m, 4 H), 2.30 (ddd, *J* = 6.7 Hz, *J* = 4.1 Hz, *J* = 3.9 Hz, 2 H), 1.68 (sept , *J* = 6.9 Hz, 2 H), 0.85 (d, *J* = 6.9 Hz, 6 H), 0.81 (d, *J* = 6.9 Hz, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.0, 135.2, 128.1, 126.0, 125.4, 117.0, 61.0, 56.0, 59.6, 42.7, 29.1, 19.2, 18.8. MS (EI) *m*/*z* 347 (100), 141 (95), 244 (90), 158 (68), 55 (60), 357 (22). Anal. Calcd for $C_{24}H_{40}N_2O_2$: C, 74.18; H, 10.38; N, 7.21. Found C, 74.20; H, 10.40; N, 7.18.

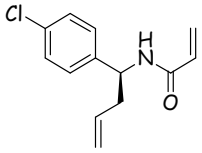


2,6-Di[(1*S*)-(1)-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]amino-3-buten-1-yl]pyridine (18): colourless oil; $[\alpha]_D^{20\tilde{}}$ -60.0 (c 0.86, $CHCl_3$). IR (neat): *v* = 3346, 3076, 2959, 1640, 1591, 1448, 1048. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (t, *J* = 7.3 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 2 H), 5.79 (m, 2 H), 5.02 (m, 4 H), 3.79 (dd, *J* = 7.1 Hz, *J* = 6.6 Hz, 2 H), 3.61 (dd, *J* = 10.8 Hz *J* = 4.1 Hz, 2 H), 3.61 (dd, *J* = 10.8 Hz, *J* = 4.4 Hz, 2 H), 2.76 (bs, 2 H), 2.46 (m, 4 H), 2.30 (ddd, *J* = 6.5 Hz, *J* = 4.4 Hz, *J* = 4.1 Hz, 2 H), 1.74 (sept, *J* = 6.8 Hz, 2 H,), 0.83 (d, *J* = 6.8 Hz, 6 H), 0.79 (d, *J* = 6.8 Hz, 6 H). ^{13}C NMR (75

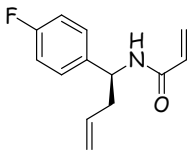
MHz, $CDCl_3$): δ = 162.4, 136.3, 135.3, 120.9, 117.3, 62.5, 61.3, 59.9, 42.0, 29.5, 19.6, 18.8. Anal. Calcd for $C_{23}H_{39}N_3O_2$: C, 70.91; H, 10.09; N, 10.79. Found C, 70.95; H, 10.11; N, 10.77.



(*S*)-*N*-(1-Phenyl-3-buten-1-yl) Propenamide (**13a**)**:** white solid; m.p. 86-86.5 °C; $[\alpha]_D^{20}$ -132.1 (c 0.5, $CHCl_3$). IR (KBr); *v* = 3258, 3071, 1651, 1627, 1584, 1414, 1247, 922. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.31 (dd, *J* = 17.2 Hz, *J* = 1.9 Hz, 1 H), 6.12 (dd, *J* = 17.2 Hz, *J* = 9.8 Hz, 1 H), 5.96 (bs, 1 H), 5.72 (m, 1 H), 5.65 (dd, *J* = 9.8 Hz, *J* = 1.9 Hz, 1 H), 5.14 (m, 3 H), 2.63 (m, 2 H). ^{13}CNMR (75 MHz, $CDCl_3$): δ = 164.8, 141.4, 133.9, 130.8, 128.6, 127.3, 126.6, 126.5, 118.2, 52.5, 40.3. MS (EI) *m*/*z* = 106 (100), 160 (90), 55 (29), 77 (13), 161 (10), 201 (M^+, 2). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found C, 77.42; H, 7.54; N, 6.93.

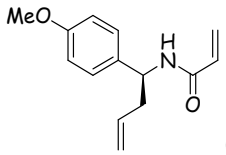


(*S*)-*N*-[1-(4-Chlorophenyl)-3-buten-1-yl) Propenamide (**13b**)**:** white solid; m.p. 125-126 °C; $[\alpha]_D^{20}$ -113.4 (c 0.48, $CHCl_3$). IR (KBr): *v* = 3294, 1658, 1631, 1545, 1406, 1296, 824. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 2 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 6.24 (dd, *J* = 16.9 Hz, *J* = 2.0 Hz, 1 H), 6.13 (dd, *J* = 16.9 Hz, *J* = 9.8 Hz, 1 H), 6.01 (d, *J* = 7.2 Hz, 1 H), 5.71 (m, 1 H), 5.59 (dd, *J* = 9.8 Hz, *J* = 2.0 Hz, 1 H), 5.07 (m, 3 H), 2.53 (d, *J* = 7.1 Hz, 1 H), 2.50 (d, *J* = 6.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 140.2, 133.5, 132.8, 130.5, 128.9, 128.5, 127.8, 126.6, 118.3, 52.1, 40.1. MS (EI) *m*/*z* = 140 (100), 194 (85), 55 (80), 142 (40), 196 (35), 129 (30), 235 (M^+, 2). Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94. Found C, 66.18; H, 6.00; N, 5.92.

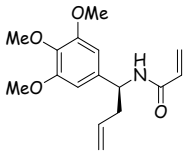


(*S*)-*N*-[1-(4-Fluorophenyl)-3-buten-1-yl) Propenamide (**13c**): white solid; m.p. 83-83.5 °C; $[\alpha]_D^{20}$ -98.1 (c 0.88, $CHCl_3$). IR (Nujol): *v* = 3292, 3076.0, 1656, 1628, 1546, 1226. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 8.7 Hz, *J* = 6.0 Hz, 2 H), 7.01 (t, *J* = 8.7 Hz, 2 H), 6.01 (d, *J* = 7.2 Hz, 1 H), 6.28 (dd, *J* = 17.1 Hz, *J* = 1.8 Hz 1 H), 6.14 (dd, *J* = 17.1 Hz, *J* = 9.9 Hz, 1 H), 5.69 (m, 1 H), 5.63 (dd, *J* = 9.9 Hz, *J* = 1.8 Hz, 1 H), 5.13 (m, 3 H), 2.57 (t, *J* = 6.9 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 161.8 (d, *J* = 227.1 Hz), 137.4, 133.7, 130.1, 128.1 (d, *J* = 6.8 Hz), 126.6, 118.2, 115.2 (d, *J* = 22.0

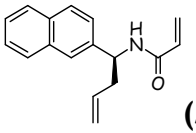
Hz), 52.1, 40.3. MS (EI) *m/z* = 124 (100), 55 (93), 178 (70), 120 (20), 95 (15), 219 (M^+, 2). Anal. Calcd for $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; N, 6.39. Found C, 70.10; H, 6.45; N, 6.37.



(*S*)-*N*-[1-(4-Methoxyphenyl)-3-buten-1-yl) l Propenamide (**13d**)**:** white solid: m.p. 124-125 °C. $[\alpha]_D^{20}$ -130.1 (c 0.83, $CHCl_3$). IR (KBr): *v* = 3318, 2958, 1656, 1625.9, 1528, 1250. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, H), 7.26 (dd, *J* = 17.0 Hz, *J* = 1.8 Hz, 1 H), 6.19 (dd, *J* = 17.0 Hz, *J* = 10.2 Hz, 1 H), 6.01 (d, *J* = 7.2 Hz, 1 H), 5.69 (m, 1 H), 5.64 (dd, *J* = 10.2 Hz, *J* = 1.8 Hz, 1 H), 5.01 (m, 3 H), 3.78 (s, 3 H), 2.58 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.7, 158.7, 134.1, 133.6, 130.8, 127.7, 126.4, 117.9, 113.9, 55.2, 52.0, 40.2. MS (EI) *m/z* 136 (100), 190 (80), 55 (20), 137 (15), 191 (10), 231 (M^+, 2). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found C, 72.52; H, 7.43; N, 6.04.

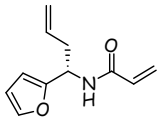


(*S*)-*N*-[1-(3,4,5-Trimethoxyphenyl)-3-buten-1-yl) Propenamide (**13e**)**:** white solid; m.p. 100-100.5 °C; $[\alpha]_D^{20}$ -103.5 (c 0.53, $CHCl_3$). IR (KBr): *v* = 3304, 3063, 2945, 1655, 1592, 1465, 1236, 1001. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.51 (s, 1 H), 6.30 (dd, *J* = 16.8 Hz, *J* = 1.9 Hz, 1 H), 6.11 (dd, *J* = 16.8 Hz, *J* = 9.7 Hz, 1 H), 5.74 (m, 1 H), 5.64 (dd, *J* = 9.7 Hz, *J* = 1.9 Hz 1 H), 5.11 (m, 3 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 2.58 (dd, *J* = 7.0 Hz, *J* = 6.1 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ. = 164.7, 153.0, 137.4, 136.9, 133.9, 130.7, 126.3, 117.8, 103.5, 60.5, 55.8, 52.8, 40.2. MS (EI) *m/z* = 196 (100), 55 (85), 250 (75), 154 (10), 291 (M^+, 5). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81; O, 21.97. Found C, 66.02; H, 7.29; N, 4.80.

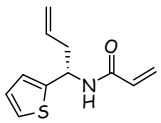


(*S*)-*N*-[1-(2-Naphthyl)-3-buten-1-yl) Propenamide (**13f**)**:** pale yellow solid; m.p. 108-108.5 °C; $[\alpha]_D^{20}$ -169.3 (c 0.51, $CHCl_3$). IR (KBr): *v* = 3448, 3326, 1652, 1622, 1522, 1349, 1242. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (m, ,4 H), 7.45 (m ,H), 6.32 (dd, *J* = 17.1 Hz, *J* = 1.8 Hz, 1H), 6.17 (dd, *J* = 17.1 Hz, *J* = 11.7 Hz, 1 H), 5.74 (m, 1 H), 5.66 (dd, *J* = 11.7 Hz, *J* = 1.8 Hz, 1 H), 5.35 (dd, *J* = 11.7 Hz, *J* = 1.8 Hz, 1 H), 5.14 (m, 2 H), 2.72 (t, *J* = 6.9 Hz, 2 H). ^{13} CNMR (50 MHz, $CDCl_3$): δ = 164.9, 150.9, 138.8, 133.2, 132.6, 130.7, 128.3, 127.8, 127.5, 126.6, 126.1, 125.8, 125.1, 124.7, 52.7, 40.1. MS (EI) *m/z* =

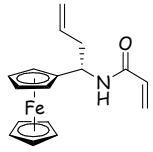
156 (100), 210 (80), 55 (55), 179 (25), 127 (21), 251 (M^+, 4). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81; O, 21.97. Found C, 66.02; H, 7.29; N, 4.80.



(*S*)-*N*-[1-(2-Furyl)-3-buten-1-yl) Propenamide (13g): yellow oil; $[\alpha]_D^{20}$ -124.3 (c 0.89, $CHCl_3$). IR (KBr): *v* = 3276, 3077, 1655, 1542, 1408, 1246, 920. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 1.8, *J* = 0.9 Hz, 1 H), 6.31 (dd, *J* = 16.9 Hz, *J* = 1.5 Hz, 1H), 6.33 (dd, *J* = 3.2, *J* = 1.9 Hz, 1 H), 6.20 (dd, *J* = 3.2, *J* = 0.9 Hz, 1 H), 6.11 (dd, *J* = 16.9 Hz, *J* = 10.0 Hz, 1 H), 5.86 (bs, 1 H), 5.73 (m, 1 H), 5.67 (dd, *J* = 16.9 Hz, *J* = 10.0 Hz, 1 H), 5.30 (dt, *J* = 8.5 Hz, *J* = 6.5 Hz, 1 H), 5.12 (m, 2 H), 2.63 (t, *J* = 6.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 153.7, 141.7, 133.4, 130.1, 126.6, 118.2, 110.1, 106.4, 46.6, 38.0. MS (EI) *m*/*z* = 96 (100), 55 (80), 150 (60), 91 (18), 191 (M^+, 2). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found C, 70.06; H, 6.87; N, 7.29.

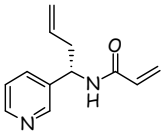


(*S*)-*N*-[1-(2-Thienyl)-3-buten-1-yl) Propenamide (13h): white solid; m.p. 75-75.5 °C; $[\alpha]_D^{20}$ -144.3 (c 0.3, $CHCl_3$). IR (neat): *v* = 3249, 1652, 1629.0, 1545, 1438, 1414, 1250. ^{1}H NMR (200MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 4.7, *J* = 1.6 Hz, 1 H), 6.96 (m, 2 H), 6.31 (dd, *J* = 17.0 Hz, *J* = 2.0 Hz, 1 H), 6.12 (dd, *J* = 17.0 Hz, *J* = 10.0 Hz, 1 H), 5.77 (m, 1 H), 5.65 (dd, *J* = 17.0 Hz, *J* = 10.0 Hz, 1 H), 5.48 (dt, *J* = 8.2 Hz, *J* = 6.8 Hz, 1 H), 5.14 (m, 2 H), 2.67 (t, *J* = 6.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 164.6, 145.1, 133.5, 130.6, 126.9, 126.8, 124.5, 124.3, 118.6, 48.2, 40.6. MS (EI) *m*/*z* = 112 (100), 55 (82), 166 (80), 135 (33), 91 (17), (M^+ 1, 1). Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; S, 15.47. Found C, 62.24; H, 6.30; N, 6.74; S, 15.42.

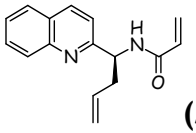


(*S*)-*N*-(1-Ferrocenyl-3-buten-1-yl) Propenamide (13i): yellow powder: m.p. 113-114 °C; $[\alpha]_D^{20}$ +33.2 (c 0.46, $CHCl_3$). IR (KBr): *v* = 3282, 1655, 1626, 1542, 1408, 1104. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 17.2 Hz, *J* = 1.8 Hz 1 H), 6.15 (dd, *J* = 17.2 Hz, *J* = 10.0 Hz, 1 H), 5.82 (m, 1 H), 5.68 (dd, *J* = 10.0 Hz, *J* = 1.8 Hz, 1 H),. 5.10 (m, 3 H), 4.17 (s, 5 H), 4.16 (m, 4 H) 3.96 (m, 1 H), 2.67 (ddd, *J* = 14.4 Hz, *J* = 4.7 Hz, *J* = 2.4 Hz, 1 H), 2.45 (ddd, *J* = 14.4 Hz, *J* = 7.2 Hz, *J* = 1.1 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.4, 134.4, 130.9, 126.3, 117.4, 90.1, 68.5, 67.7, 67.4, 66.5, 47.4, 40.3. MS (EI) *m*/*z* = 214 (100), 309 (M^+, 95), 121 (90), 116 (80), 238 (71), 56 (69), 268 (68).

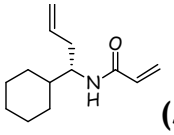
Anal. Calcd for $C_{19}H_{24}FeNO$: C, 67.47; H, 7.15; Fe, 16.51; N, 4.14. Found C, 67.13; H, 7.16; Fe, 16.46; N, 4.12.



(*S*)-*N*-[1-(3-Pyridyl)-3-buten-1-yl) Propenamide (13j): white solid; m.p. 66-66.5 °C; $[\alpha]_D^{20}$ –99.0 (c 0.44, $CHCl_3$). IR (KBr): *v* = 3302, 3051, 1655, 1629, 1542, 1411, 1242. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 8.53 (d, *J* = 5.1 Hz, 1 H), 7.32 (dd, *J* = 8.1 Hz, *J* = 5.1 Hz, 1 H), 6.31 (dd, *J* = 16.9 Hz, *J* = 1.6 Hz, 1 H), 6.14 (dd, *J* = 16.9 Hz, *J* = 10.1 Hz, 1 H), 5.70 (m, 1 H), 5.69 (dd, *J* = 10.1 Hz, *J* = 1.6 Hz, 1 H), 5.17 (m, 3 H), 2.64 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ =:165.2, 147.9, 137.5, 134.5, 133.2, 130.4, 126.3, 123.2, 118.1, 118.1, 50.7, 39.7. MS (EI) *m/z* = 107 (100), 161 (77), 55 (50), 130 (28), 147 (15), 79 (14), 201 ($M^{+\tilde{}}$ 1, 1). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found C, 71.38; H, 7.00; N, 13.80.

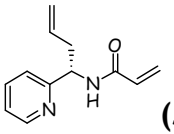


(*S*)-*N*-[1-(2-Quinolyl)-3-buten-1-yl) Propenamide (13k): light yellow solid; m.p. 105-105.5 °C; $[\alpha]_D^{20}$ ~-137.2 (c 0.23, $CHCl_3$). IR (KBr): *v* = 3284, 1655, 1626, 1541, 1408, 1243. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H) , 7.84 (d, *J* = 8.1 Hz, 1 H), 7.74 (dd, *J* = 8.4 Hz, *J* = 1.4 Hz, 1 H), 7.56 (dd, *J* = 8.1 Hz, *J* = 1.4 Hz, 1 H), 7.50 (d, *J* = 6.7 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 6.35 (m, 2 H),), 5.73 (m, 1 H), 5.70 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1 H), 5.43 (m, 1 H), 5.03 (d, *J* = 6.7 Hz, 2 H), 2.85 (dd, *J* = 15.8 Hz, *J* = 6.7 Hz, 1 H), 2.75 (dd, *J* = 15.8 Hz, *J* = 6.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.2, 159.1, 147.2, 136.1, 132.6, 130.5, 129.0, 128.3, 127.0, 125.7, 119.6, 117.7, 53.0, 39.7. MS (EI) *m/z* = 15 (100), 211 (66), 55 (38), 129 (28), 180 (23), 197 (18), 252 (M^+, 6). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.31; H, 6.41; N, 11.07.

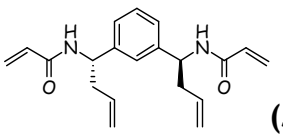


(*S*)-*N*-(1Cyclohexyl-3-buten-1-yl) Propenamide (13l): white powder; m.p. 135-136 °C. $[\alpha]_D^{20}$ +197.7 (c 0.48, $CHCl_3$). IR (KBr): *v* = 3274, 3076, 2916, 1656, 1626, 1559, 1251. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.27 (dd, *J* = 16.9 Hz, *J* = 2.1 Hz, 1 H), 6.01 (dd, *J* = 16.9 Hz, *J* = 9.6 Hz 1 H), 5.74 (m, 1 H), 5.64 (dd, *J* = 9.6 Hz, *J* = 2.1 Hz, 1 H). 5.04 (m, 2 H), 3.96 (m, 1 H),), 2.33 (ddd, *J* = 14.4 Hz, *J* = 4.7 Hz *J* = 2.4 Hz, 1 H), 2.15 (ddd, *J* = 14.4 Hz, *J* = 7.2 Hz, *J* = 1.1 Hz, 1 H), 1.9-1.6 (m, 5 H), 1.5-0.8 (m, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.2, 134.7, 131.2, 126.0, 117.5, 52.9, 41.2, 36.3, 29.6, 28.6,

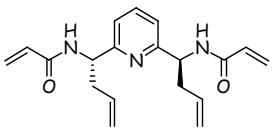
29.3, 26.1. MS (EI) *m/z* = 166 (100), 55 (75), 95 (55),112 (50), 70 (48), 124 (40). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found C,74.44; H, 10.23; N, 6,74.



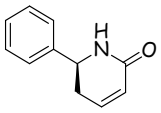
(*S*)-*N*-[1-(2-Pyridyl)-3-buten-1-yl) Propenamide (13m): white solid; m.p. 61-61.5 °C; $[\alpha]_D^{20}$ −38.7 (c 0.31, $CHCl_3$). IR (KBr): *v* = 3302, 3051, 1655, 1629, 1542, 1411, 1242. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 4.0 Hz, 1 H), 7.74 (d, *J* = 6.6 Hz, 1 H), 7.49 (dt, *J* = 7.8 Hz, *J* = 1.3 Hz, 1 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 7.03 (dt, *J* = 6.6 Hz, *J* = 1.3 Hz, 1 H), 6.09 (m, 2 H), 5.54 (m, 1 H), 5.40 (m, 1 H), 5.11 (q, *J* = 6.6 Hz, 1 H), 4.85 (d, *J* = 12.6 Hz, 2 H), 2.51 (t, *J* = 6.6 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.6, 159.3, 148.6, 136.3, 133.4, 130.5, 125.9, 122.1, 122.0, 117.6, 53.4, 39.8. MS (EI) *m/z* 107 (100), 161 (90), 55 (28), 130 (21), 79 (14), 147 (10), 203 (M^+ + 1, 1). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found C, 72.18; H, 7.01; N, 13.80.



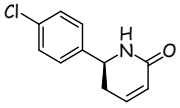
(*S,S*)-1,3-Di[1-(propenoylamino)-3-buten-1-yl]benzene (19): white solid; m.p. 138-139 °C; $[\alpha]_D^{20}$ −203.3 (c 0.7, $CHCl_3$). IR (KBr): *v* = 3253, 3067, 1650, 1226, 1550, 1411, 1247, 989, 958, 920. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26 (m, 4 H), 6.31 (dd, *J* = 16.7 Hz, *J* = 1.8 Hz 2 H), 6.13 (dd, *J* = 16.7 Hz, *J* = 9.8 Hz, 2 H), 5.94 (m, 2 H), 5.76 (m, 2 H), 5.66 (dd, *J* = 9.8 Hz, *J* = 1.8 Hz, 2 H), 5.13 (m, 6 H), 2.61 (t, *J* = 7.0 Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 141.9, 133.4, 130.8, 128.7, 126.4, 125.7, 125.0, 117.9, 52.6, 40.2. MS (EI) *m/z* 55 (100), 229 (80), 283 (70), 158 (30), 133 (20). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found C, 72.18; H, 7.01; N, 13.80.



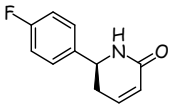
(*S,S*)-2,6-Di[1-(propenoylamino)-3-buten-1-yl]pyridine (20): white solid; m.p. 155-156 °C; $[\alpha]_D^{20}$ -175.5 (c 0.22, $CHCl_3$). IR (KBr): *v*. 3305, 3044, 1658, 1631, 1545, 1422, 1241. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63 (t, *J* = 7.6 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 6.24 (dd, *J* = 16.9 Hz, *J* = 2.0 Hz 2 H), 6.13 (dd, *J* = 16.9 Hz, *J* = 9.8 Hz, 2 H), 6.01 (d, *J* = 7.4 Hz, 1 H), 5.59 (dd, *J* = 9.8 Hz, *J* = 2.0 Hz, 1 H), 5.63 (m, 2 H), 5.25 (dd, *J* = 7.4 Hz, *J* = 6.6 Hz 2 H), 5.03 (m, 2 H), 2.67 (t, 4 H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.8, 158.8, 137.3, 133.4, 130.9, 126.5, 120.5, 118.2, 53.3, 40.2. MS (EI) *m/z* = 284 (100), 55 (92), 156 (33), 134 (29), 230 (18), 325 (M^+, 3). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found C, 73.90; H, 7.48; N, 8.62.



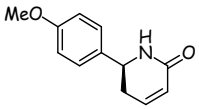
(*S*)-5,6-Dihydro-6-phenylpyridin-2(1H)-one (14a): White solid; m.p. 117-117.5 °C; IR (KBr): *v* = 3221, 2925, 2852, 1672, 1609, 1449, 1320, 1141, 817; $[\alpha]_D^{20}$ -216.5 (c 0.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 6.55 (ddd, *J* = 10.0 Hz, *J* = 5.0 Hz, *J* = 3.3 Hz, 1 H), 6.0 (d, *J* = 10.0 Hz, 1 H), 4.71 (dd, *J* = 10.6 Hz, *J* = 6.3 Hz, 1 H), 2.53 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 141.1, 140.0, 128.8, 128.1, 126.3, 124.5, 55.6, 32.9. MS (EI) *m/z* = 174.2 $(M + H)^+$, 347.1 $(2 M + H)^+$, 369.2 $(2 M + Na)^+$. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found C, 76.14; H, 6.42; N, 8.08.



(*S*)-5,6-Dihydro-6-(4-chlorophenyl)pyridin-2(1H)-one (14b): white solid; m.p. 126-127 °C. $[\alpha]_D^{20}$ ~-193.1 (c 0.82, $CHCl_3$). IR (KBr) *v* = 3187, 2930, 1670, 1611, 1493, 1089, 823. ^{1}HNMR (300 MHz, $CDCl_3$): δ =7.41 (d, *J* = 8.6 Hz, 2H, ArH), 7.35 (d, *J* = 8.6 Hz, 2 H), 6.65 (ddd, *J* = 9.9 Hz, *J* = 2.5 Hz, *J* = 1.1 Hz, 1 H), 6.28 (bs, 1 H),. 6.03 (d, *J* = 9.9 Hz, 2 H), 4.77 (dd, *J* = 10.6 Hz, *J* = 9.9 Hz, 1 H), 2.66 (ddd, *J* = 17.9 Hz, *J* = 5.9 Hz *J* = 1.1 Hz, 1 H), 2.50 (ddd, *J* = 17.9 Hz, *J* = 10.6 Hz, *J* = 2.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.45, 139.8, 139.7, 129.0, 127.7, 124.6, 54.9, 32.8. MS (ES) *m/z* = 415.0 (2 M + H)$^+$, 437.1 (2 M + Na)$^+$. Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found C, 63.82; H, 4.87; N, 6.72.

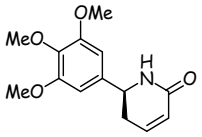


(*S*)-5,6-Dihydro-6-(4-fluorophenyl)pyridin-2(1H)-one (14c): white solid; m.p. 121-122 °C; $[\alpha]_D^{20}$ ~-206.0 (c 0.20, $CHCl_3$). IR (KBr): *v* = 3184, 3049, 2941, 1667, 1603, 1512, 1414, 1219, 834. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.2 Hz, J_{F-H} = 5.7 Hz , 2 H), 7.04 (dd, *J* = 8.2 Hz, J_{F-H} = 7.8 Hz , 2 H), 6.60 (ddd, *J* = 10.0 Hz, *J* = 3.2 Hz, *J* = 1.1 Hz, 1 H), 6.1 (bs, 1 H), 5.97 (d, *J* = 10.0 Hz, 2 H), 4.71 (dd, *J* = 11.0 Hz, *J* = 5.9 Hz, 1 H), 2.57 (ddd, *J* = 17.8 Hz, *J* = 5.9 Hz *J* = 1.1 Hz, 1 H), 2.45 (ddd, *J* = 17.8 Hz, *J* = 11.0 Hz, *J* = 3.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 162.4 (d, *J* = 248.5 Hz), 139.9, 136.9, 128.0 (d, *J* = 8.1 Hz), 124.5, 115.6 (d, *J* = 21.5 Hz), 54.7, 33.0. MS (ES) *m/z* = 192.3 $(M + H)^+$, 383.3 $(2 M + H)^+$, 405.1 $(2 M + Na)^+$. Anal. Calcd for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33. Found C, 68.09; H, 5.27; N, 7.31.

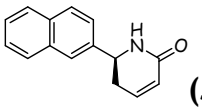


(*S*)-5,6-Dihydro-6-(4-methoxyphenyl)pyridin-2(1H)-one (14d): white solid; m.p. 138-139 °C. $[\alpha]_D^{20}$ -188.6 (c 0.36, $CHCl_3$). IR (KBr): *v* = 3183, 2963, 1682,

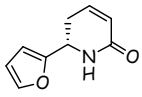
1614, 1512, 1252, 1026, 836. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.60 (ddd, *J* = 9.9 Hz, *J* = 3.4 Hz, *J* = 1.3 Hz 1 H), 6.1 (bs, 1 H). 5.96 (d, *J* = 9.9 Hz, 2 H), 4.67 (dd, *J* = 10.9 Hz, *J* = 6.2 Hz, 1 H), 3.79 (s, 3 H), 2.50 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 159.2, 140.1, 132.9, 127.5, 124.3, 114.0, 55.1, 54.9, 32.9. MS (ES) *m/z* = 407.3 $(2\ M + H)^+$, 429.1, $(2\ M + Na)^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found C, 79.87; H, 6.44; N, 6.90.



(*S*)-5,6-Dihydro-6-(3,4,5-trimethoxyphenyl)pyridin-2(1H)-one (14e): whitish oil; $[\alpha]_D^{20}$ ~-181.7 (c 0.20, $CHCl_3$). IR (neat): *v* = 3188, 2956, 1689, 1622, 1505, 1249, 1030, 840. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60 (ddd, *J* = 9.9 Hz, *J* = 2.8 Hz, *J* = 1.4 Hz 1 H), 6.55 (s, 2 H), 5.97 (d, *J* = 9.9 Hz, 2 H), 5.91 (bs, 1 H). 4.64 (dd, *J* = 11.4 Hz, *J* = 5.7 Hz, 1 H), 3.83 (s, 6 H), 3.81 (s, 3 H), 2.54 (ddd, *J* = 17.4 Hz, *J* = 5.7 Hz *J* = 1.4 Hz, 1 H), 2.46 (ddd, *J* = 17.9 Hz, *J* = 11.4 Hz, *J* = 2.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 153.4, 140.2, 136.6, 124.4, 103.2, 60.7, 56.0, 33.2. MS (ES) *m/z* = 264.1 $(M + H)^+$, 528.3 $(2\ M + 2\ H)^+$, 549.3 $(2\ M + Na)^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found C, 64.06; H, 6.54; N, 5.30.

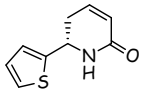


(*S*)-5,6-Dihydro-6-(2.naphthyl)pyridin-2(1H)-one (14f): white solid; m.p. 137-138 °C. $[\alpha]_D^{20}$ -132.0 (c 2.6, $CHCl_3$). IR (KBr): *v* = 3288,2945, 2876, 2852, 1676, 1660, 1601, 1482, 1380, 1350, 1322, 1226, 1148, 1136, 809, 763, 741, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (m, 4 H), 7.51 (m, 3 H), 6.64 (m, 1 H),. 6.04 (d, *J* = 9.9 Hz, 1 H), 5.89 (bs, 1 H), 4.77 (dd, *J* = 10.2 Hz, *J* = 6.3 Hz, 1 H), 2.64 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 140.1, 138.4, 133.2, 133.1, 128.9, 127.9, 127.7, 126.5, 126.3, 125.4, 124.5, 124.0, 55.8, 32.9. MS (ES) *m/z* = 224.1, $(M + H)^+$, 447.1, $(2\ M + H)^+$, 469.2, $(2\ M + Na)^+$. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found C, 80.75; H, 5.89; N, 6.24.

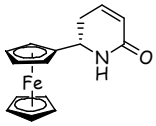


(*S*)-5,6-Dihydro-6-furylpyridin-2(1H)-one (14g): white powder; m.p. 98-99 °C; $[\alpha]_D^{20}$ -93.0 (c 0.49, $CHCl_3$). IR (KBr:): *v* = 3289, 3117, 2950, 1671, 1593, 1475, 804. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 1.6 Hz, 1 H), 6.8 (bs, 1H), 6.55 (dt, *J* = 10.0 Hz, *J* = 4.1 Hz, 1 H), 6.29 (dd, *J* = 3.0 Hz. *J* = 1.6 Hz , 1 H), 6.21 (d, *J* = 3.0 Hz, 1 H), 5.57 (dd, *J* = 10.0 Hz, *J* = 1.8 Hz, 1 H), 4.74 (t, *J* = 7.1 Hz, 1 H), 2.62 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.0, 153.4, 142.1, 139.5, 124.3, 110.2, 106.3, 48.6, 28.5, MS (ES)

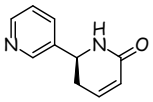
m/*z* = 164.1 $(M + H)^+$, 327.0 $(2 M + H)^+$], 349.1 $(2 M + Na)^+$. Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found C, 65.75; H, 5.55; N, 8.56.



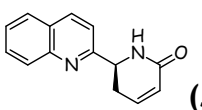
(*S*)-5,6-Dihydro-6-thienylpyridin-2(1H)-one (14h): white solid, m.p. 109-110 °C, $[\alpha]_D^{20}$ -151.8 (c 1.2, $CHCl_3$). IR (KBr): *v* = 3478, 2924, 1671, 1608, 1407, 1303, 1124. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 5.3 Hz, 1 H), 6.98 (m, 2 H), 6.64 (dt, *J* = 10.1 Hz, *J* = 4.0, 1 H), 6.02 (d, *J* = 10.1 Hz, 1 H), 5.01 (dd, *J* = 9.4 Hz, *J* = 6.4 Hz, 1 H), 2.69 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.8, 144.4, 139.9, 126.8, 125.1, 125.0, 124.7, 51.1, 33.3. MS (ES) *m*/*z* = 180.1 $(M + H)^+$, 359.0 $(2 M + H)^+$, 381.0 $(2 M + Na)^+$. Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found C, 60.45; H, 5.08; N, 7.80; S, 17.82.



(*S*)-5,6-Dihydro-6-ferrocenylpyridin-2(1H)-one (14i): red solid; m.p. 143-144 °C; $[\alpha]_D^{20}$ +94.3 (c 0.66, $CHCl_3$). IR (KBr): *v* = 1675, 1611, 1420, 1315, 1105, 814. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.65 (ddd, *J* = 9.9 Hz, *J* = 5.6 Hz, *J* = 2.7 Hz, 1 H), 5.96 (d, *J* = 9.9 Hz, 1 H), 5.88 (bs, 1 H), 4.38 (dd, *J* = 12.0 Hz, *J* = 5.5 Hz, 1 H), 4.21 (m, 5 H), 4.18 (m, 4 H), 2.48 (ddd, *J* = 17.7 Hz, *J* = 5.6 Hz, *J* = 5.5 Hz, 1 H), 2.31 (ddd, *J* = 17.7 Hz, *J* = 12.0 Hz, *J* = 2.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.2, 150.9, 140.4, 124.5, 89.4, 68.5, 68.2, 66.7, 65.1, 50.6, 33.2. Anal. Calcd for $C_{17}H_{21}FeNO$: C, 65.61; H, 6.80; Fe, 17.95; N, 4.50. Found C, 64.85; H, 6.82; Fe, 17.90; N, 4.48.

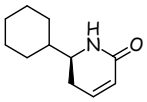


(*S*)-5,6-Dihydro-6-(3-pyridyl)pyridin-2(1H)-one (14j): yellowish oil; $[\alpha]_D^{20}$ -143.9 (c 1.7, $CHCl_3$). IR (neat) *v* = 3187, 3056, 2928, 1688, 1611, 1431, 812. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.57 (m, 2 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.31 (dd, *J* = 8.0 Hz, *J* = 4.9 Hz, 1 H), 6.60 (ddd, *J* = 9.8 Hz, *J* = 5.0 Hz, *J* = 3.5 H, 1 H), 6.53 (bs, 1 H), 6.0 (dd, *J* = 9.8 Hz, *J* = 1.3 Hz, 1 H), 4.78 (dd, *J* = 10.1 Hz, *J* = 6.1 Hz, 1 H), 2.66 (ddd, *J* = 17.5 Hz, *J* = 6.1 Hz *J* = 5.0 Hz 1H), 2.50 (ddd, *J* = 17.5 Hz, *J* = 10.1 Hz, *J* = 6.1 Hz, 1 H). $^{13}CNMR$ (50 MHz, $CDCl_3$): δ = 166.3, 149.6, 148.2, 139.7, 136.6, 133. 9, 124.7, 123.7, 53.2, 32.5. MS (ES) *m*/*z* = 175.2 $(M + H)^+$, 349.1 $(2 M + H)^+$, 371.2 $(2 M + Na)^+$. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found C, 69.09; H, 5.81; N, 16.01.

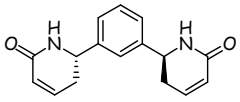


(*S*)-5,6-Dihydro-6-(2-quinolyl)pyridin-2(1H)-one (14k): white solid; m.p. 107-107.5 °C; $[\alpha]_D^{20}$ ~-39.6 (c 0.33, $CHCl_3$). IR (KBr): *v* = 3184, 3052, 2925, 1681, 1609,

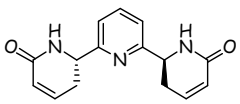
1423, 1101, 808. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.31 (dd, *J* = 7.2 Hz, *J* = 6.6 Hz, 1 H), 7.7 (dd, *J* = 8.1 Hz, *J* = 6.6 Hz, 1 H), 7.59 (dd, *J* = 8.4 Hz, *J* = 6.6 Hz, 1 H,), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.01 (bs, 1 H), 6.71 (ddd, *J* = 9.8 Hz, *J* = 6.3 Hz, *J* = 2.7 Hz, 1 H), 6.11 (d, *J* = 9.8 Hz, 1 H), 5.06 (dd, *J* = 11.7 Hz, *J* = 5.4 Hz, 1 H), 2.92 (ddd, *J* = 17.7 Hz, *J* = 6.3 Hz, *J* = 5.4 Hz, 1 H), 2.66 (ddd, *J* = 17.7 Hz, *J* = 11.7 Hz *J* = 2.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 158.3, 147.2, 139.6, 137.3, 130.0, 129.1, 127.5, 127.3, 126.8, 125.4, 117.8, 55.5, 30.6. MS (ES) *m*/*z* = 225.2 $(M + H)^+$, 449 $(2 M + H)^+$, 471.0 $(2 M + Na)^+$. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 75.03; H, 5.40; N, 12.44.



(*S*)-5,6-Dihydro-6-cyclohexenylpyridin-2(1H)-one (14l): white powder; m.p. 137-137.5 °C; $[\alpha]_D^{20}$ -67.0 (c 0.32, $CHCl_3$). IR (KBr): *v* = 3248, 2928 1652, 1545, 1415, 1250. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.65 (ddd, *J* = 9.8 Hz, *J* = 5.2 Hz, *J* = 3.3 Hz 1 H), 6.35 (bs, 1 H), 5.96 (dd, *J* = 9.8 Hz, *J* = 1.9 Hz ,1 H), 3. 36 (ddd, *J* = 11.8 Hz, *J* = 6.1 Hz, *J* = 1.0 Hz, 1 H), 2.26 (m, 2 H), 1.73 (m, 4 H), 1.41 (m, 3 H), 1.09 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 140.6, 124.2, 55.4, 41.5, 28.6, 28.5, 26.4, 26.1, 25.8. MS (ES) *m*/*z* = 180.2 $(M + H)^+$, 381.2 $(2 M + H)^+$. Anal. Calcd for $C11H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found C, 72.58; H, 10.00; N, 7.80.



(*S*,*S*)-1,3-Di[5,6-dihydropyridin-2(1H)-one-6-yl]benzene (21): white solid; m.p. 175-176 °C; $[\alpha]_D^{20}$ ~-270.0 (c 0.94, $CHCl_3$). IR (KBr): *v* = 3223, 3042, 1678, 1604, 1420, 1305, 1126, 812. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (m, 3 H), 7.32 (dt, *J* = 6.8 Hz, *J* = 1.6 Hz, 1 H), 7.21 (dd, *J* = 6.8 Hz, *J* = 1.4 Hz, 2 H), 6.57 (ddd, *J* = 9.9 Hz, *J* = 5.4 Hz, *J* = 2.9 Hz, 2 H), 5.93 (d, *J* = 9.8 Hz, 2 H), 4.75 (dd, *J* = 11.3 Hz, *J* = 5.7 Hz, 2 H), 2.56 (ddd, *J* = 17.9 Hz, *J* = 5.4 Hz, *J* = 5.4 Hz, 2 H) 2.41 (ddd, *J* = 17.9 Hz, *J* = 11.3 Hz, *J* = 2.9 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.0, 141.9, 139.8, 128.8, 126.0, 124.4, 123.7, 55.1, 32.8. MS (ES) *m*/*z* = 270.2 $(M + 2 H)^+$, 561.2 $(2 M + 2 H)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found C, 72.01; H, 6.03; N, 10.40.



(*S*,*S*)-2,6-Di[5,6-dihydropyridin-2(1H)-one-6-yl]pyridine (22): white solid, m.p. 79-80 °C. $[\alpha]_D^{20}$ ~-99.3 (c 0.5 , MeOH); IR (KBr): *v* = 3386, 3067, 2925, 2848, 1654, 1596, 1458, 1313, 1124. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.60 (m, 3 H), 7.32 (dt, *J* = 6.8 Hz, *J* = 1.6 Hz, 1 H), 7.21 (dd, *J* = 6.8 Hz, *J* = 1.4 Hz, 2 H), 6.57 (ddd, *J* = 9.9 Hz, *J*

= 5.4 Hz, *J* = 2.9 Hz, 2 H), 5.93 (d, *J* = 9.8 Hz, 2 H), 4.75 (dd, *J* = 11.3 Hz, *J* = 5.7 Hz, 2 H), 2.56 (ddd, *J* = 17.9 Hz, *J* = 5.4 Hz, *J* = 5.4 Hz, 2 H), 2.41 (ddd, *J* = 17.9 Hz, *J* = 11.3 Hz, *J* = 2.9 Hz, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.7, 160.1, 140.4, 138.3, 125.3, 119.9, 54.9, 30.16.MS (ES) *m/z* 270.2 (M + H)+, 539.3 (2 M + H)+. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found C, 65.97; H, 5.62; N, 15.55.

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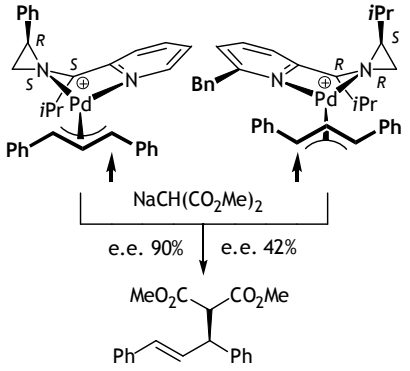
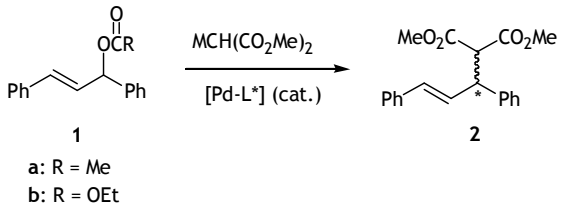
Chapter 5

Steric effects in the enantioselective allylic alkylation catalyzed by cationic (η^3-allyl)palladium complexes bearing chiral pyridine-aziridine ligands.



5.1 Introduction:

C_2-Symmetric enantiopure *N*,*N*-bidentate ligands have been widely used in the asymmetric Pd-catalyzed allylic substitution reactions, like the reaction of 1,3-diphenylpropenyl acetate **1a** with the anion of dimethyl malonate, in the presence of allylpalladium chloride dimer to give the substitution product **2** which has become the prototype reaction for test of new chiral ligands.

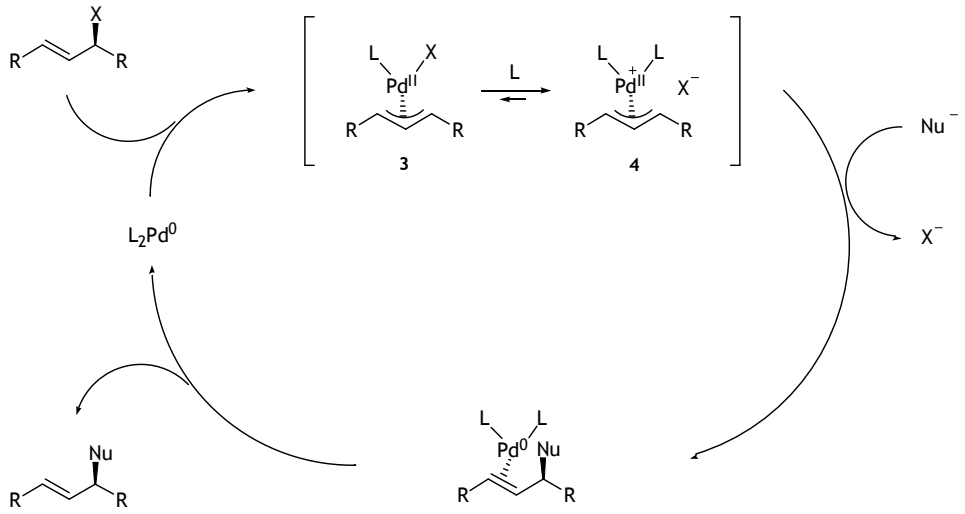


1

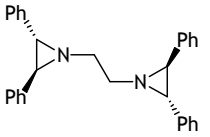
a: R = Me
b: R = OEt

2

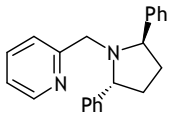
The accepted mechanism for this reaction involves first the oxidative addition of a Pd(0) specie on the allylic substrate to yield a η^3 allyl-Pd(II) complex. The equilibrium between the neutral complex **3** and the cationic specie **4** depends on many factors like the solvent and the nature of the ligand, but with bidentate ligands it is usually shifted to the side of the cationic complex. This is highly reactive towards soft nucleophiles, which attack at the less substituted allylic terminus leading to a η^2-olefin-Pd^0 complex, then to the final product and a Pd(0) complex that restarts another catalytic cycle.



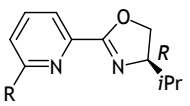
In literature are described many examples of ligands that can efficiently catalyze this reaction in an asymmetric fashion, and a few of them contain the pyridine or aziridine ring. For example the C_2-symmetric bis(aziridine) **5**[1] afforded a complete enantioselectivity, while the pyridine derivative **6**[2] gave a 64% e.e.. In C_1-symmetric 2-(2'-pyridyl)oxazolines **7a,b**[4] and **8**[4c,5] a remarkable effect of the substituent in both rings was observed; particularly, the substitution of Ph for the *i*-Pr group in the oxazoline was beneficial, as a better e.e. was provided by **8** with the same pyridine substituent (R = H). Most importantly, the presence of a (chiral) bulky substituent at the pyridine-C_6, or the presence of a benzo[*b*]-fused ring as in **9**, caused an increase of the enantioselectivity.[4,5] It should be observed that the ligands **7-9** form a rigid five-membered chelation ring in the cationic (η^3-allylic)Pd complexes but also six-membered chelation rings like those derived from the ligands **10-12** have been studied. In the case of 8-quinoline-oxazolines **8**, an unexpected effect of the substitution was observed, as with R = Me[6] and the benzo[*b*]-derivative[4] the opposite enantiomer of **2** was produced. Similarly, the 2-(quinolylmethyl)oxazoline **12** displayed the opposite enantioselectivity with respect to **11**.[6]



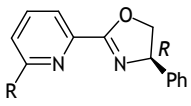
5: e.e. >99%



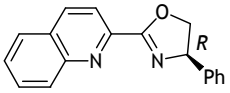
6: e.e. 64%



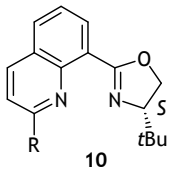
7
a: R = H, e.e 24% (*R*);
b: R = Me, e.e. 70% (*R*)



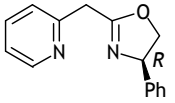
8
a: R = H, e.e. 50% (*R*) (55%);
b: R = Me, e.e. 74% (*R*) (74%);
c: R = CH_2OH, e.e. 88% (*R*);
d: R = (*S*)-CH(*t*Bu)OMe,
e.e. >99% (*R*)



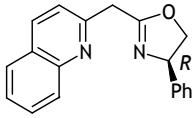
9: e.e. 73% (*R*)



10
a: R = H, e.e. 77% (*S*);
b: R = Me, e.e. 78% (*R*)

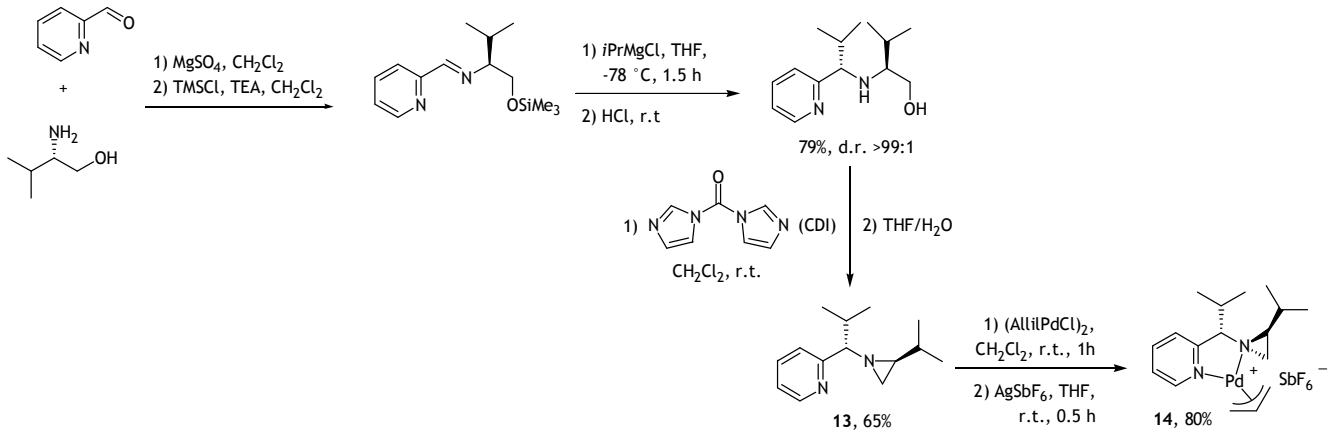


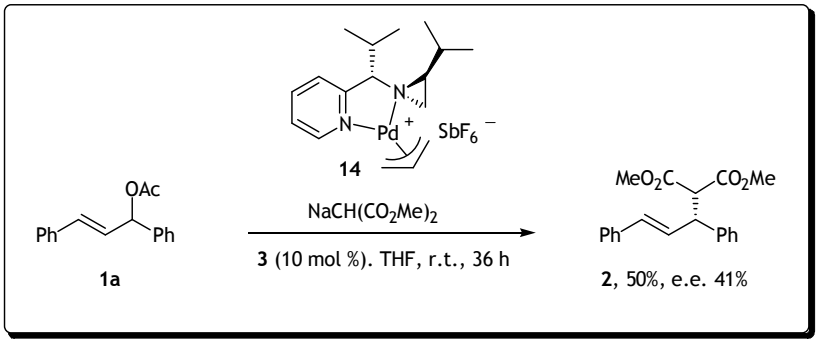
11: e.e. 16% (*R*)



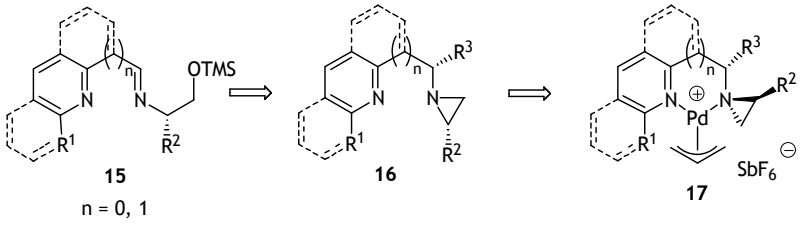
12: e.e. 78% (*S*)

We observed that (*N*,*N*')* ligands containing both the pyridine and aziridine rings were not described in the literature and envisioned a simple two-step route to 1-[1(*S*)-(2-pyridyl)alkyl]-2(*S*)-isopropylaziridines **13** from *N*-(2-pyridylmethylidene) (*S*)-valinol.[7] In a preliminary report we have described the preparation of **13** and its cationic η^3-allylpalladium complex **14**, which is more effective than the free base in the above mentioned Pd-catalysed allylic substitution reaction, providing (*R*)-**2** with moderate yield and 41% e.e. (Table 1, entry 1).[8] The ligand **13** differs from **5-12** for the presence of a stereocentre in the carbon chain linking the two nitrogen atoms, besides the one present on the aziridine carbon. The two stereocentres in **13** have a combined role compelling the aziridine nitrogen to assume the *R* configuration when forming the Pd complex, as shown by the X-ray structure analysis of **14**. This happens to avoid the severe interaction of the two *i*Pr substituents, which instead would occur in the alternative complex with the *S* configuration.





Since then, we have directed our efforts to the preparation of other C_1-symmetrical (*N*,*N*')* ligands and their palladium complexes, having general structure **16** and **17**, respectively, by the same previously applied route that involves the initial organometallic addition step to the imine **15** to give the 1,2-aminoalcohol **16**, from which the aziridine ring is constructed. This route is flexible, as it allows to vary the ligand skeleton and the size of the Pd-chelated ring (starting from the proper aldehyde) and all the substituents, like, for example the heterocyclic rings (ring-substituted aza-heteroaromatic aldehyde and chiral 1,2-aminoalcohol) and the tether connecting them (organometallic reagent). Similarly, the influence of a new substituent R^1 or a benzo[*b*]-fused pyridine ring can be studied preparing the ligand from a suitable aldehyde. As a corollary of this study, owing to the low reactivity of the acetate **1** in the reaction catalyzed by **14**, we have checked the more reactive 1,3-diphenyl-2-propenyl ethyl carbonate **1b** as the substrate in the same substitution reaction.



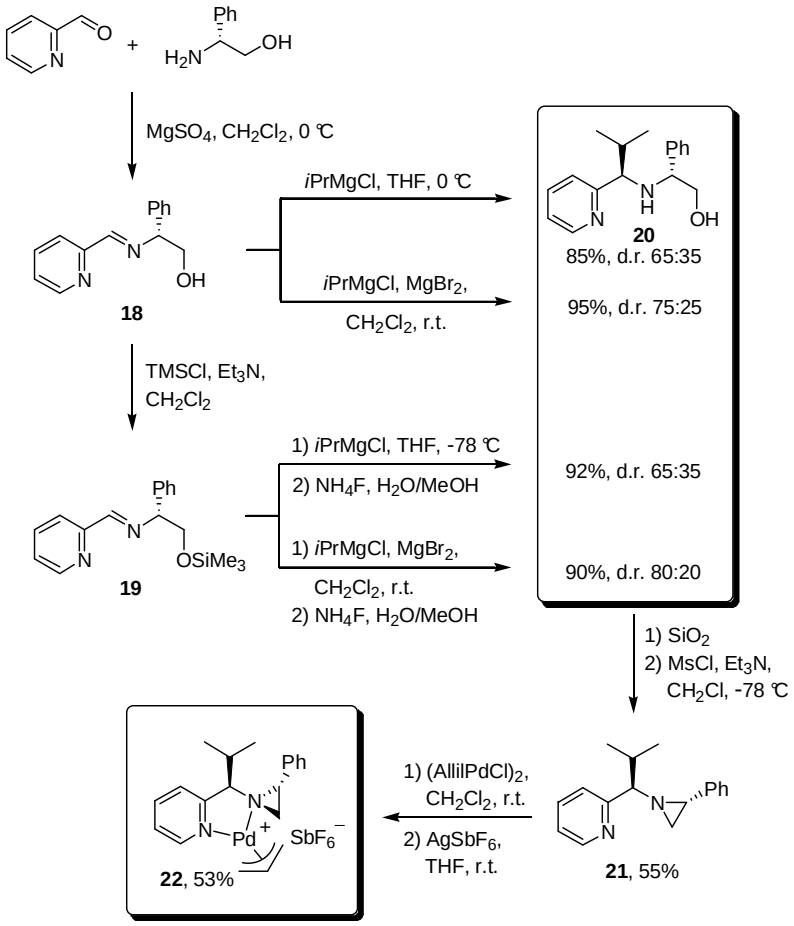
5.2. Results and Discussion

5.2.1. Influence of the aziridine ring substituent

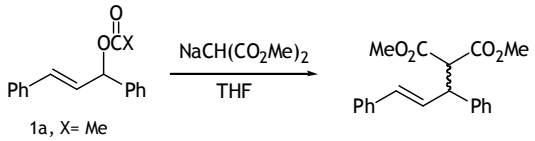
In order to determine the effect of the aziridine C2-substituent on the enantioselectivity we have chosen to replace the *i*Pr group, present in **13**, with a different group. This has been accomplished by preparing the free imine **18** and the *O*-protected one **19**, from 2-pyridinaldehyde and (*R*)-phenylglycinol, and optimising the preparation of the amino-

alcohol **20** from them. Although phenylglycinol has been widely exploited for the diastereoselective addition of organometallic reagents to imines,[9] in our hands the addition of *i*-PrMgCl to **18** in THF at 0 °C gave the secondary amines **20** with moderate sterocontrol. No attempt was made to separate the main (*S*,*S*)-diastereomer. The experimental conditions used by Spero[10] for similar Grignard reactions on 2-pyridyl ketimines were then applied to **18**, involving the use of CH_2Cl_2 as the solvent and the presence of $MgBr_2$.[10] By this way, a 95% yield and a 75:25 d.r. (^{1}H NMR spectroscopy) were obtained for **20**. Also the addition of *i*PrMgCl to the *O*-protected imine **19** in THF at ~78 °C gave **20** with a moderate diastereoselectivity (65:35), but a better d.r. (80:20) was finally obtained applying the Spero protocol to the protected imine **19** and the main diastereomer of **20** was isolated pure in 45% yield by column chromatography of the reaction mixture.

The conversion of the amino alcohol **20** to the aziridine **21** by treatment with carbonyl diimidazole (CDI)[8,11] was not satisfactory. In this case, a better result was achieved by the reaction with mesyl chloride and triethylamine at −78 °C, after which **21** was isolated with 55% yield. The cationic (η^3-allyl)-Pd complex **22** was then prepared by the routine procedure.



The complex **22** (10 mol%) was used for the catalytic allylation of sodium dimethyl malonate with the acetate **1a**, but almost no reaction was observed after 1 day at 25 °C. However, using the carbonate **1b**, almost complete conversion (TLC) after 12 h at 25 °C in THF was observed and the product (*S*)-**2** was isolated by column chromatography with 70% yield and e.e. 90% (Table 1, entry 3). It is noteworthy that using **14** as the catalyst (5 mol%) the malonate **2** was obtained with 85% yield from the carbonate **1b** after only 3 h at 25 °C, but with lower e.e. (19%, entry 2) with respect to the reaction on the acetate **1a** (entry 1); unfortunately, almost no reaction took place with **1b** at 0 °C. The reaction of the carbonate **1b** with dimethyl malonate in the presence of 10 mol% of either sodium hydride[12] and complex **22** at 25 °C stopped after a few hours, at which time a black Pd precipitate was formed; then the product **2** was detected in poor amounts by T.L.C. analysis. The reaction of **1b** with sodium dimethyl malonate (1.5 equiv) in the presence of allylpalladium chloride dimer (5 mol%) and ligand **21** (10 mol%), forming in situ the reactive complex **22**, gave (*S*)-**2** with 74% yield and e.e. 86% (entry 4). On the other hand the reaction of **1b** with dimethyl malonate (2.5 equiv), bis(trimethylsilyl)acetamide (BSA, 3 equiv.), potassium acetate (1 mol%) and the palladium complex **22** (10 mol%) gave a largely incomplete conversion to (*S*)-**2**, which was isolated after 12 h with only 33% yield although with high e.e. (90%). It should be underlined that the two complexes **14** and **22** have opposite chirality consequently, they induced the same sense of asymmetric induction in the formation of (*R*)-**2** and (*S*)-**2**, respectively.



1a, X= Me
1b, X= OEt

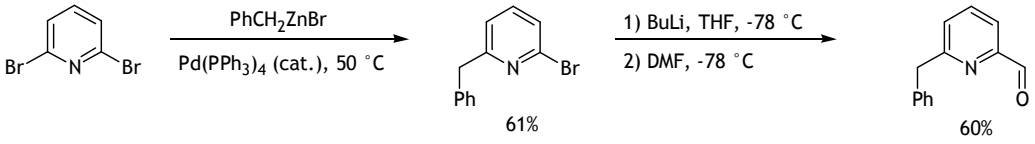
Entry	Substrate	Catalyst (eq.)	Time (h)	Product	Yield %	Ee%
1	1a	**14**(0.1)	36	(*R*)-**2**	50	42
2	1b	**14** (0.05)	3	(*R*)-**2**	85	19
3	1b	**22** (0.1)	12	(*S*)-**2**	70[a]	90
4	1b	**22** (0.1) [b]	12	(*S*)-**2**	74	86

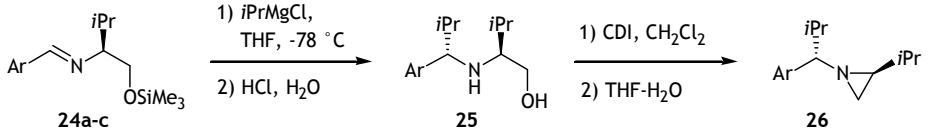
[a] Almost no reaction occurred at 0°C or when using 10mol-% of sodium hydride. [b] Catalyst generated in situ with 0.05 eq. of $(allylPdCl)_2$

5.2.2. Influence of the ligand skeleton and C_6-pyridine substituent

We aimed to assess the effect of the modified *N*,*N*-ligand skeleton or pyridine-substitution pattern on the enantioselectivity of the substitution reaction, we synthesized the imines **24a-c** from commercially available 2- and 8-quinolinaldehydes and prepared 6-benzyl-2-pyridinaldehyde. We wished to study the effect of the steric interaction between the pyridine-fused benzene ring or the C6-benzyl substituent with the phenyl group of the η^3-allylic ligand in the reactive allylic complex. On the other hand, a six membered Pd-chelation is formed from the ligand **26b** derived from **24b**, possibly resulting in a modified structure of the allylic complex.

The addition of *i*PrMgCl to **24a** was plagued by poor chemoselectivity, affording the β-aminoalcohol **25a** with 25% yield after chromatographic separation from several unidentified by-products and its diastereomer (d.r. 75:25 was determined by GC-MS analysis of the crude product). A more selective addition of the same Grignard reagent was observed to the 8-quinolineimine **24b** (d.r. 85:15) and the pure diastereomer **25b** was isolated with 38% yield. Finally, the imine **24c** was prepared from 6-benzyl-2-bromopyridine[13] by bromine-lithium exchange at low temperature, followed by reaction with DMF. The reaction of **24c** with *i*PrMgCl gave the aminoalcohol **25c** with good yield and diastereoselectivity (d.r. 90:10), and the pure diastereomer was isolated with 56% yield by column chromatography. The aziridines **26a-c** and their cationic (η^3-allyl)Pd complexes **27a-c** were readily prepared by the routine sequence with good yields.





24a-c

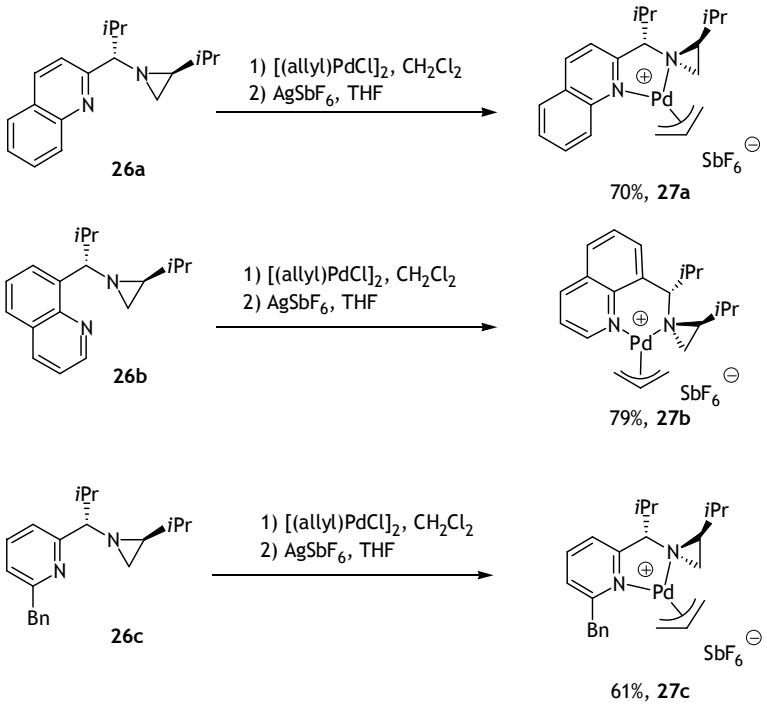
a: Ar = 2-quinolyl
b: Ar = 8-quinolyl
c: Ar = 6-benzyl-2-pyridyl

25

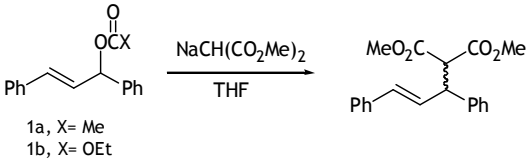
a: d.r. 75:25 (crude), 25% (pure)
b: d.r. 85:15 (crude), 38% (pure)
c: d.r. 90:10 (crude), 56% (pure)

26

a: 63%;
b: 65%;
c: 59 %



The reactions carried out on the acetate **1a** catalysed by the complexes **27a-c** gave unexpected results. A low enantioselectivity for (*R*)-**2** was obtained using **27a** (e.e. 4%, entry 5) while an inversion of the enantioselectivity was observed in the reaction catalysed by **27b**: in fact, (*S*)-**2** was prevalently formed, although with low e.e. (23%, entry 6). In both cases, the pyridine substituent caused an increase of the reaction time needed to achieve a satisfactory conversion. An even more sluggish reaction was observed using the 6-benzylpyridine derivative **27c**, so that in this case we worked on the more reactive carbonate **1b** and obtained (*S*)-**2** with reasonable yield and moderate enantioselectivity (e.e. 47%, entry 7). When the same reaction was performed at higher temperature (50 °C) the reaction rate considerably increased and (*S*)-**2** was isolated with 75% yield, but slightly lower e.e. (37%, entry 8).



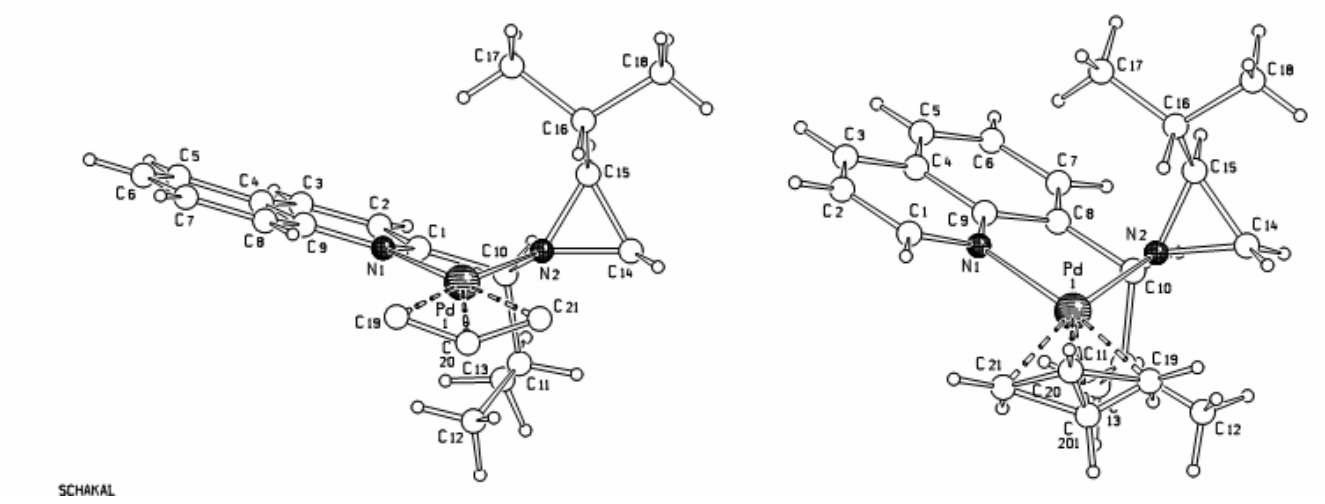
Entry	Substrate	Catalyst (eq.)	Time (h)	Product	Yield %	Ee%
5	1a	**27a** (0.1)	36	(*R*)-**2**	22	4
6	1a	**27b** (0.1)	24	(*S*)-**2**	35	23

7	1b	**27c** (0.1)	18	(*S*)-**2**	43	42
8	1b	**27c** (0.1)	6[a]	(*S*)-**2**	75	35

[a] The reaction was performed at 50 °C.

5.2.3. X-Ray studies of (η^3-1,3-diphenylallyl)Pd complexes. Tentative explanation of the divergent enantioselectivity

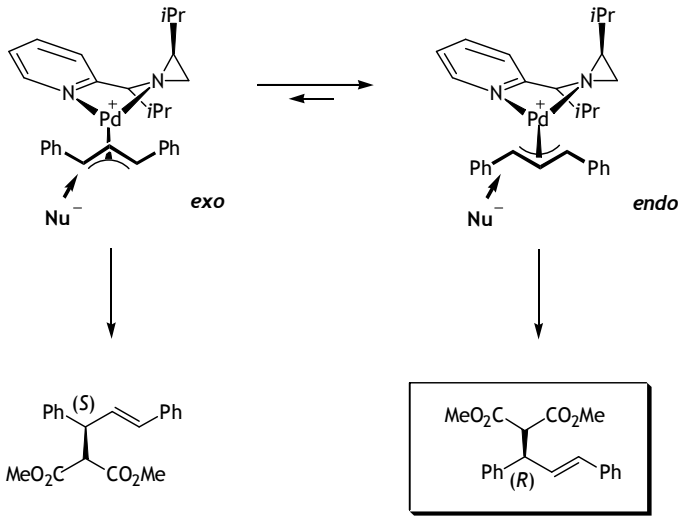
In order to explain the stereochemical outcomes of the reaction we started studying the x-ray structure of the (*N*,*N*')*(η^3-allyl)palladium salts **14** and **27a,b** that we prepared. All the complexes showed the palladium atom in a distorted square-planar geometry, also it is important to note the unique conformation of the cationic nitrogen atom, that is *R* for the complexes **14**, **27a**,**b**,**c** derived from (*S*)-valinol, and *S* for the complex **22** derived from (*R*)-phenylglycinol, this avoids the steric interaction between the *i*Pr group present in the tether linking the nitrogen atoms and the aziridine substituent (*i*Pr or Ph). Another important point is that all the structures showed a longer carbon-palladium bond anti to the nitrogen of the aziridine ring (Pd-C3) than to the pyridine (Pd-C1). All the (*N*,*N*')*(η^3-allyl)palladium salts are present, even in the crystal structure in a mixture of exo/endo rotamers and that ratio is usually different in solution as witnessed from their ^{1}H-NMR spectra. X-Ray analyses of the re-crystallised salts **27a**,**b** showed structures similar to that of **14**.[8] However, two independent cations are present in the crystals of the 2-quinoline derivative **27a**, and in both of them the *endo*-allyl rotamer predominates. In the crystal of the 8-quinoline derivative **27b**, featuring a six-membered Pd-chelation ring, an *exo*/*endo* ratio 56:44 of the allyl rotamers was observed. It is noteworthy that the ligands in the salts **14** and **27a,b** present similar envelope or puckered conformations.



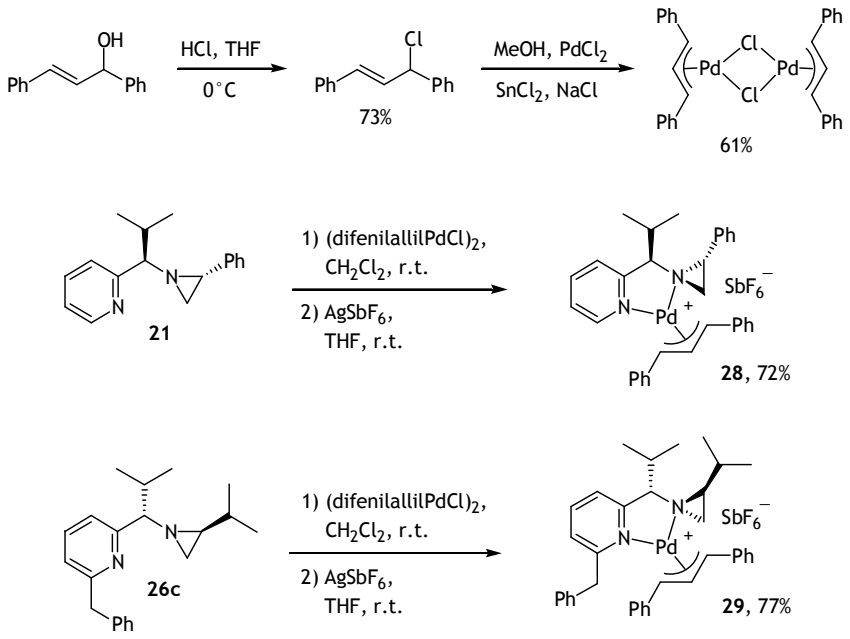
Bond	Distance (Å)
Pd- C19	2.148
Pd-C21	2.106
Pd-N1	2.145
Pd-N2	2.101

Bond	Distance (Å)
Pd- C21	2.150
Pd-C19	2.118
Pd-N1	2.126
Pd-N2	2.098

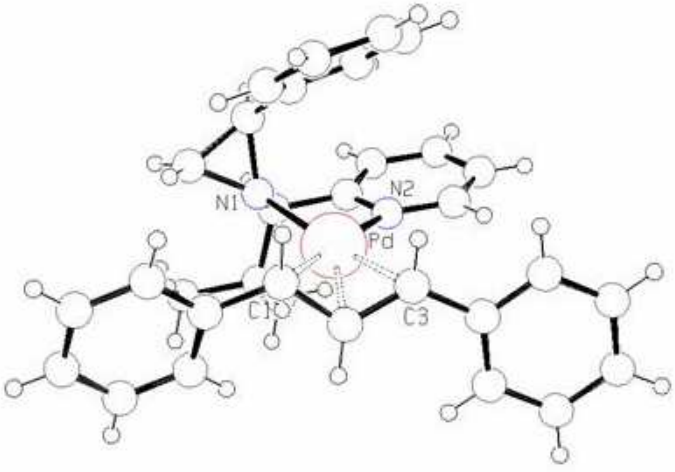
If we think that these all these features characterize also the (η^3-1,3-diphenylallyl)Pd complexes which are the real intermediates of the reaction, we can explain the enantioselectivity observed by the attack of the nuclefile (malonate anion) at the most electrophilic carbon atom (anti to the aziridine ring) of the prevalent endo rotamer. This model worked fine to describe the results obtained with all the complexes but couldn't explain the inverted enantioselectivity obtained with catalyst **27c** with respect to **22**.



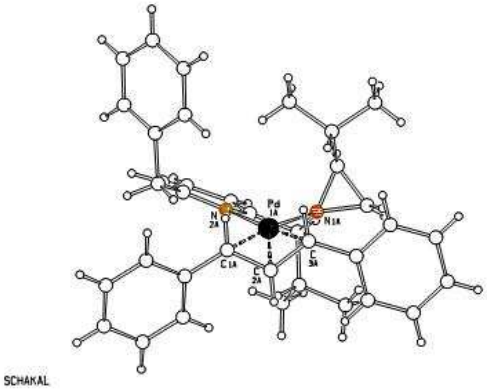
With the hope to find important clues for the understating of the course of these reactions, we prepared the corresponding cationic (η^3-1,3-diphenylallyl)Pd complexes as hexafluoroantimonate salts **28** and **29**, which are the possible intermediates in the enantio-discriminating steps.



X-Ray diffraction analysis showed that the structures of these complexes are similar to each other as well as to those of **14**[8] and **27a**,**b**.[14] However, only the *endo* rotamers of the 1,3-diphenylallyl ligand were present in **28** and **29**. For clarity, the aziridine and pyridine nitrogen atoms are indicated as N_A and N_P, respectively, and the allylic carbons C_A (*trans* to aziridine) and C_P (*trans* to pyridine).

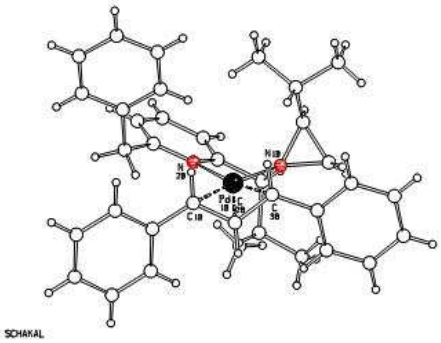


Bond	Distance (Å)
Pd-N_1	2.135
Pd-N_2	2.133
Pd-C_1	2.134
Pd-C_3	2.166



Bond	Distance (Å)
Pd_{1A}-N_{1A}	2.133
Pd_{1A}-N_{2A}	2.180
Pd_{1A}-C_{1A}	2.210
Pd_{1A}-C_{3A}	2.140

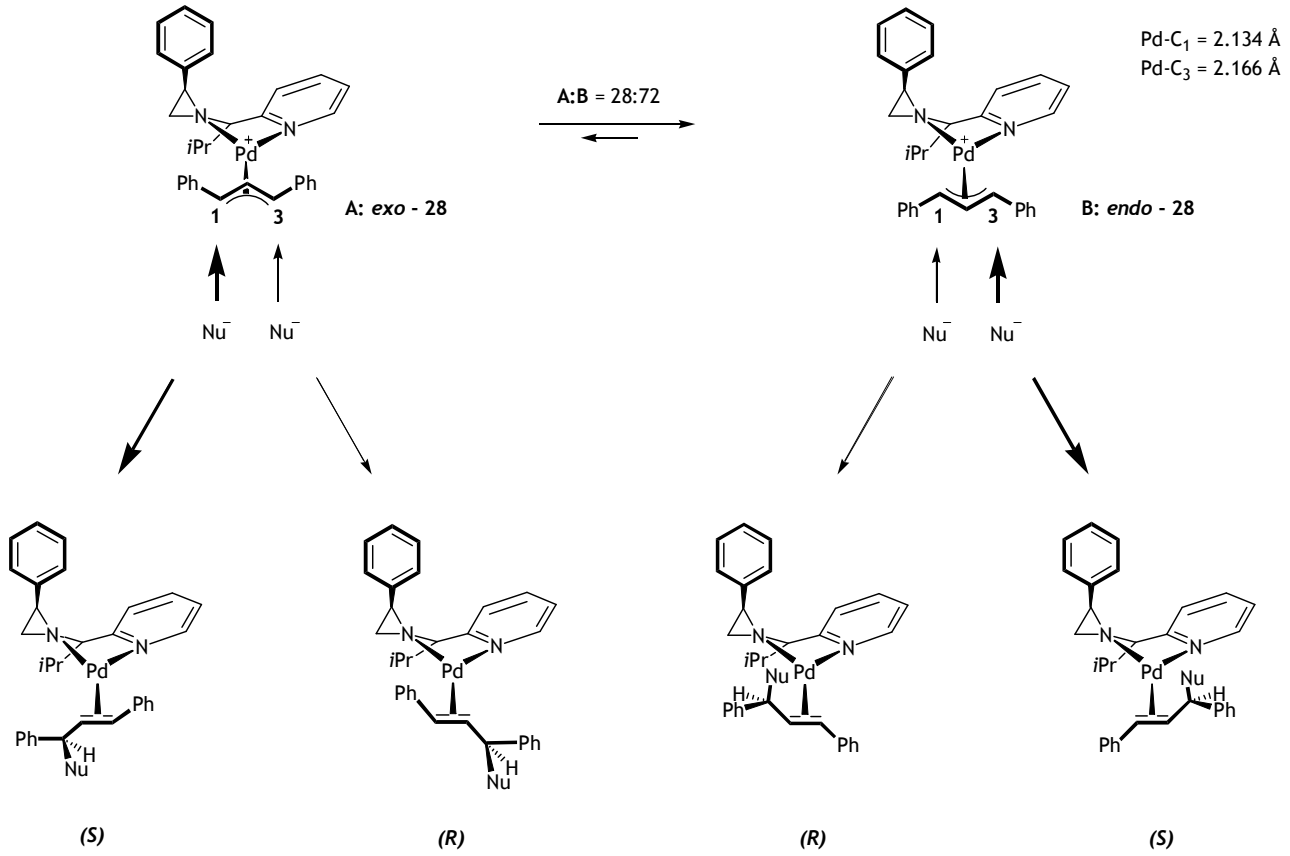
Bond	Distance (Å)
Pd_{1B}-N_{1B}	2.152
Pd_{1B}-N_{2B}	2.200
Pd_{1B}-C_{1B}	2.230
Pd_{1B}-C_{3B}	2.166



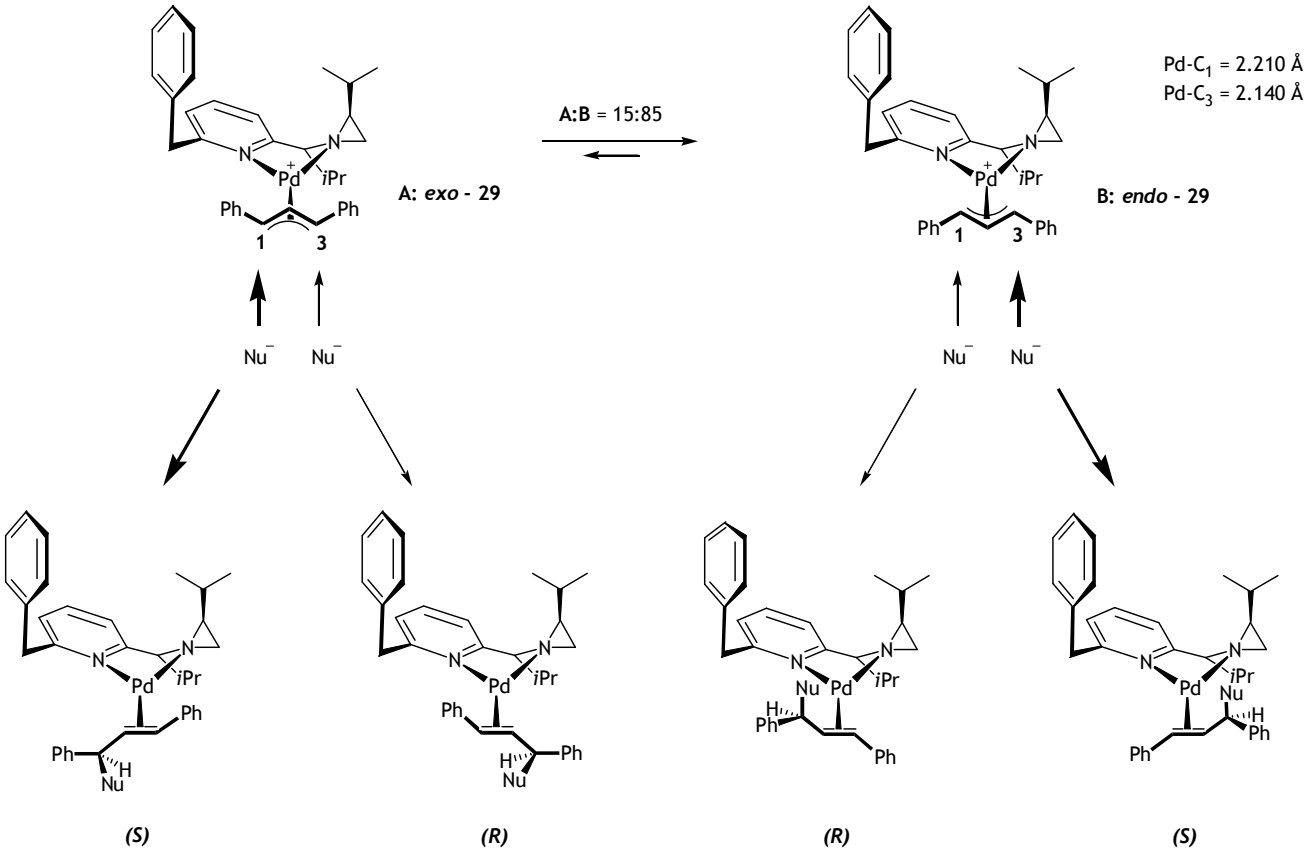
In the (η^3-1,3-diphenylallyl)]Pd complex **28**, two independent cations are present, the Pd-N_P bonds are in the range 2.180-2.200(5) Å, that are considerably longer than the Pd-N_A bonds (2.133-2.152(6) Å). This is noteworthy because N_P and NA use sp^2 and sp3-type orbitals, respectively. The lengths of the two Pd-NA bonds in the calculated structure of the complex [**3**-(η^3-1,3-diphenylallyl)Pd][SbF_6] were 2.131 and 2.134 Å,[1b,f] which are comparable to the values observed in **28** and **29**. On the contrary, in the reported X-ray structure of an [(*N*,*N*')(η^3-1,3-diphenylallyl)Pd]$^+$ cation, the metal formed a longer bond with pyrrolidine (2.15 Å) with respect to pyridine (2.08 Å).[2a] Moreover, the two Pd-N bonds in the [(sparteine)(η^3-1,3-diphenylallyl)Pd]$^+$ cation were 2.19 and 2.24 Å long.[16] Hence, it appears that the aziridine nitrogen generally forms with palladium cation a bond shorter than other sp^3-hybridised nitrogen atoms.

It should also be considered that the complexes **28** and **29** in $CDCl_3$ solution are present as *syn,syn-endo*/*syn,syn-exo* mixtures (72:28 and 85:15, respectively), and that in no case *anti,syn* allyl species were detected. The *endo*/*exo* ratios and the Pd-C bond lengths are

determined by steric effects like the non-bonding interactions of the (*N*,*N*')* and allyl ligands, whereas electronic effects are not relevant. In the hypothesis that the *endo* and *exo* rotamers have the same reactivity and undergo a completely regioselective attack, the e.e.'s of the product would be correlated to the *endo*/*exo* ratio. For example, this was true in reactions catalysed by 8-(2-oxazoline)quinoline ligands.[20] The high enantioselectivity observed for (*S*)-**2** in the reaction catalyzed by the complex **28** is the result of two convergent factors: the prevalence of the rotamer *endo*-**28** in solution, and the relatively low activation energy of the transition state deriving from the nucleophilic attack to the more electrophilic CA allylic terminus and leading to the η2-complex.



In the case of complex **29**, the relative ratio and reactivity of *endo* and *exo* rotamers must be considered.[21] The different reactivity is probably associated to the relative stability of the late transition states leading to the alternative η^2-complexes which are precursors of the product **2**. It should be observed that the formation of the η^2-complex by attack to the less abundant rotamer *exo*-**29** occurs by "preferential rotation"[22] and does not suffer for severe steric interactions, contrary to the alternative η2-complex which would be derived from *endo*-**29**.



5.3 Conclusions

We have investigated the synthetic route to enantiopure C_1-symmetric *N*,*N*'-bidentate ligands carrying either a 1,2-disubstituted aziridine and an aza-aromatic ring. The ligands were prepared from imines derived pyridine- and quinolinealdehydes and optically pure β-amino alcohols. The ligands were then converted to the [(*N*,*N*')*(η^3-allyl)Pd][SbF_6] complexes, which were used as catalysts in the allylic substitution reaction of 1,3-diphenyl-2-propenyl esters with sodium dimethyl malonate in THF.[16,23] Although the synthetic route to the ligand proved to be more efficient and stereoselective starting from (*S*)-valinol as the chiral precursor, it was observed that the analogous ligand prepared from (*R*)-phenylglycinol was considerably more enantioselective in the catalytic application (e.e. 90%), as a consequence of the more demanding steric effect of the phenyl substituent in the aziridine ring, which is oriented towards the Pd-allylic ligand. On the other hand, structural variations in the starting heterocyclic aldehyde, the capability of the ligand to form either a five- or six-membered ring with palladium, the substitution pattern in the

aza-heteroaromatic ring had relevant effects on either reactivity and stereocontrol. Especially, inversion of enantioselectivity was observed using the ligand bearing a 6-benzyl-substituted pyridine. The X-ray diffraction studies of two [(*N*,*N*')*(η3-1,3-diphenylallyl)Pd][SbF_6] complexes which afforded the most marked difference in enantioselectivity showed the similarity of their structures and the presence of only the *endo* allylic rotamers, at a difference with the unsubstituted allyl Pd complexes. Hence, the solid state structure does not always correspond to the more reactive conformer in solution, and the steric effects of the different skeleton or substituents on the regio- and stereoselectivity are not easily evaluated.[24] Interestingly, the Pd-N(aziridine) bonds in most allylic complexes studied are shorter than the Pd-N(pyridine) bonds.

Lack of reactivity was observed with cyclohexenyl acetate, as previously reported for the reaction catalysed by the bis(aziridine) **5**.[1] The moderate efficiency of the alkylation reactions catalysed by our ligands/complexes can be attributed to the weakness of the Pd-N(pyridine) bond(s), which affects the stability of the chelated [(*N*,*N*')*(¤^{3}-allyl)Pd]+ cations. Similarly, the absence of a π-acceptor N ligand in (*N*,*N*')* probably does not allow the effective stabilization/dissolution of the Pd(0) species which are formed by nucleophilic attack to the intermediate cationic complex. With regard to this, it should be worth studying the effect of electron-withdrawing substituents on the pyridine ring of the ligand, particularly at C4 where steric effects are absent.

Experimental Section

General Remarks

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent in N_2 atmosphere before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), CH_2Cl_2 (P_2O_5). Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. ^1H NMR spectra were recorded on a Varian Gemini instrument at 300 or 200 MHz for samples in $CDCl_3$ which was stored over Mg: ^1H chemical shifts are reported in ppm relative to $CHCl_3$ (δ_H 7.27) and *J*-values are given in Hz. MS spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Chromatographic separations were performed on columns of SiO_2 (Merck, 230-400 mesh) at medium pressure. The following materials were purchased from Aldrich: *n*BuLi (1.6 M in hexanes), *i*PrMgCl (2 M in THF), $[(allyl)PdCl]_2$, $AgSbF_6$, 3-methyl-2-butenyl bromide, 2-pyridinaldehyde, 2-quinolinaldehyde, (*S*)-valinol, (*S*)-phenylglycinol, 1,1'-

carbonyldiimidazole, thionyl chloride. 8-Quinolinealdehyde was prepared from 8-methylquinoline by oxidation with SeO_2.[25] η^3-(1,3-Diphenylallyl)palladium chloride dimer was prepared from the allylic chloride by reaction with $PdCl_2$-$SnCl_2$-NaCl in DMF following a procedure described for the preparation of different η^3-allylic Pd(II) complexes.[26] All the organometallic reactions were performed in a flame-dried apparatus under a static atmosphere of dry N_2.

Preparation of the imines

The imines were prepared in the 5 mmol scale by the previously described procedure[27] and used avoiding purification.

(*S*)-*N*-[(2-Pyridyl)methylidenelphenylglycinol (18).[28] Yellow oil: 100%. $[\alpha]_D^{20}$ +19.6 (c 0.83, $CHCl_3$). We observed a 55:45 mixture of imine and 1,3-oxazolidine by ^1H NMR in $CDCl_3$ (200 MHz): δ = 8.49 (s, 1 H, CH=N), 5.65 (s, 1 H, NCHO). The ^1H NMR spectra in $CDCl_3$ and THF-d_8 have been partially described.[28]

(*S*)-*N*-[(2-Pyridyl)methylidene]-*O*-trimethylsilylphenylglycinol (19). Yellow oil: 84%. $[\alpha]_D^{20}$ −15.5 (c, 0.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (d, *J* 4 Hz, 1 H, pyridine), 8.43 (s, 1 H, CH=N), 8.15 (d, *J* = 8 Hz, 1 H, Py), 7.73 (t, *J* = 8 Hz, Py), 7.55-7.20 (m, 6 H, Py and Ph), 4.50 (m, 1 H, C*H*Ph), 3.84 (m, 2 H, CH_2O), 0.0 (s, 9 H, $SiMe_3$). GC.-MS: *m*/*z* (relative intensity) 195 (100, M^+ – CH_2OSiMe_3), 92 (30), 73 (18), 66 (12), 163 (10), 298 (M^+ – 1, 4).

(*S*)-*N*-[(2-Quinolyl)methylidene]-*O*-trimethylsilylvalinol (24a): Yellow oil; 94%. $[\alpha]_D^{20}$ −23.2 (c 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.48 (s, 1 H, CH=N), 8.15 (m, 3 H, quinoline), 7.90-7.50 (m, 3 H, quinoline), 3.92 (dd, *J* = 4.2 and 10.5 Hz, 1 H, CH_2O), 3.75 (dd, *J* = 8.1 and 10.5 Hz, 1 H, CH_2O), 3.18 (m, 1 H, CHN), 2.0 (m. 1 H, C*H*Me_2), 0.95 (2 d, *J* 6.7 Hz, 6 H, CH*Me*$_2$), 0.05 (s, 9 H, $SiMe_3$). GC-MS: *m*/*z* (relative intensity) 211 (100, M^+ – CH_2OSiMe_3), 169 (42), 142 (34), 73 (31), 181 (25), 271 (10), 115 (5), 299 (5, M^+ – Me)

(*S*)-*N*-[(8-Quinolyl)methylidene]-*O*-trimethylsilylvalinol (24b). Yellow oil: 98%; $[\alpha]_D^{20}$ −32 (c, 1.80, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.58 (s, 1 H, CH=N), 8.98 (dd, *J* = 2.0 and 4.2 Hz, 1 H, quinoline), 8.46 (dd, *J* = 1.6 and 7.4 Hz, 1 H, quinoline), 8.19 (dd, *J* = 4.8 and 8.0 Hz, 1 H, quinoline), 7.90 (dd, *J* 1.40 and 8.0 Hz, 1 H, quinoline), 7.60 (t, *J* = 7.4 Hz, 1 H, quinoline), 7.44 (dd, *J* = 4.4 and 8.4 Hz, 1 H, quinoline), 3.95 (dd, *J* = 6.6 and 10.6 Hz, 1 H, CH_2O), 3.75 (dd, *J* = 7.8 and 10.2 Hz, 1 H, CH_2O), 3.25 (m, 1 H, N-CH), 2.05 (m, 1

H, C*H*Me$_2$), 1.00 (d. *J* = 7.0 Hz, 6 H, CH*Me*$_2$), 0.07 (s, 9 H, SiMe$_3$). GC-MS: *m*/*z* (relative intensity) 155 (100), 211 (38, M$^{+\cdot}$ CH$_2$OSiMe$_3$), 142 (36), 156 (18), 73 (17), 299 (M$^+$ – Me, 4).

(*S*)-*N*-[(6-Benzyl-2-pyridyl)methylidene]-*O*-trimethylsilylvalinol (24c): 6-Benzyl-2-bromopyridine was prepared from 2,6-dibromopyridine according to the reported procedure:[13] yellowish oil (61%). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 7.48-7.18 (m, 7 H, Ar), 7.00 (d, *J* = 7.0 Hz, 1 H, Py), 4.15 (s, 2 H, CH$_2$); MS: *m*/*z* (relative intensity) 248 (100), 246 (95), 247 (44), 167 (43), 249 (41), 166 (27), 168 (24), 65 (11), 83 (10), 139 (9). To the solution of this compound (1.36 g, 5.5 mmol) in THF (8 ml) cooled at –78 °C was slowly added *n*BuLi (1.6 M in hexanes, 3.44 ml, 5.5 mmol) while magnetically stirring. The mixture was stirred for 1 h at –78 °C, then dry DMF (0.66 ml) was directly added to the solution. After stirring was continued for 1 h, H$_2$O (10 ml) was added and the organic phase was extracted with Et$_2$O (3 × 10 mL). The collected organic layers were dried (Na$_2$SO$_4$) and concentrated to leave an oily residue. Chromatography on a silica gel column, eluting with cyclohexane-ethyl acetate 10:1, gave 6-benzyl-2-pyridinealdehyde as an oil (0.65 g, 60%): ^{1}H-NMR (200 MHz, CDCl$_3$): ¤ 10.10 (s. 1 H, CHO), 7.80 (m, 2 H, Py), 7.48-7.10 (m, 6 H, Ar), 4.27 (s, 2 H, CH$_2$); MS: *m*/*z* (relative intensity) 196 (100), 197 (28), 167 (21), 168 (15), 166 (14), 91 (9), 65 (7), 115 (5). The imine **24c** was then obtained from the aldehyde by the previously described procedure as a yellowish oil (1.08 g, 90%). [α]$_D^{20}$ –9.4 (c 0. 38, CHCl$_3$). ^{1}H NMR (200 MHz, CDCl$_3$): δ = 8.32 (s, 1 H, CH=N), 7.89 (d, *J* = 7.6 Hz, 1 H, Py),7.60 (t, *J* = 7.6 Hz, 1 H, Py), 7.40-7.17 (m, 5 H, Ph), 7.08 (d, *J* = 7.8 Hz, 1 H, Py), 4.20 (s, 2 H, CH$_2$), 3.87 (dd, *J* = 4.4 and 10.2 Hz, 1 H, CH$_2$O), 3.67 (t, *J* = 10.2 Hz, 1 H, CH$_2$O), 3.09 (m, 1 H, NC*H*CH$_2$O), 1.97 (m, 1 H, C*H*Me$_2$), 0.94 and 0.93 (2 d, *J* = 6.6 Hz, 6 H, CH*Me*$_2$), 0.06 (s, 9 H, SiMe$_3$). GC-MS: *m*/*z* (relative intensity) 251 (100), 73 (26), 209 (18), 183 (11), 221 (10), 354 (M$^+$, 9), 339 (7), 311 (5).

Preparation of secondary amines by addition of *i*PrMgCl to imines

***N*-[1(*R*)-(2-pyridyl)-2-methylpropyl]-(*R*)-phenylglycinol (20)**: To the solution of the imine **18** (1.782 g, 6 mmol) in CH$_2$Cl$_2$ (60 mL), cooled at 0 °C, was added anhydrous MgBr$_2$ (1.656 g, 9 mmol), and the mixture was stirred for 1 h, meanwhile the temperature rose to 20 °C. Then *i*PrMgCl (2 M in Et$_2$O, 9.0 mL, 18 mmol) was added during 10 min and the mixture was further stirred 3 h, then quenched with sat. NaHCO$_3$ (20 mL). The organic layer was separated and the organic material was extracted from the aqueous phase with CH$_2$Cl$_2$ (3 ×

20 mL). The collected organic layers were concentrated and the residue was treated with NH_4F (2.0 g) in MeOH-H_2O (1:1, 20 mL) for 6 h, then solid NaOH was added to reach pH 11 and the organic material was extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried (Na_2SO_4) and concentrated to leave an oily residue. The diastereomeric ratio 80:20 was determined by GC-MS and ^{1}H NMR spectroscopy. Chromatography on a SiO_2 column eluting with cyclohexane-ethyl acetate mixture gave the compound **20** as a pure diastereomer: yellowish oil: 0.736 g, (45%);. $[\alpha]_D^{20}$ –23.3 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, *J* = 4.8 Hz, 1 H, Py), 7.46 (t, *J* = 7.6 Hz, 1 H, Py), 7.2-7.0 (m, 6 H, Ar), 7.95 (d, *J* = 7.6 Hz, Py), 3.8-3.5 (m, 3 H, CHCH2), 3.41 (d, *J* = 7.2 Hz, 1 H, C*H*i*Pr*), 2.01 (m, 1 H, C*H*Me2), 1.25 (broad, 2 H, OH and NH), 1.05 and 0.79 (2 d, *J* = 6.9 Hz, CH*Me*$_2$). Found: C 75.30, H 8.10, N 10.31; $C_{17}H_{22}N_2O$ requires: C 75.52; H 8.20, N 10.36%. The product decomposed during GC-MS analysis. The minor diastereomer was not isolated in a pure state by column chromatography..

Preparation of the amines 25a-c

The reagent *i*PrMgCl (6 mmol) was added to the solution of the imine (3 mmol) in THF (10 mL), magnetically stirred and cooled at –78 °C. After 1.5 h, the reaction mixture was quenched by adding saturated aq $NaHCO_3$ (10 mL) and the organic phase was extracted with ether (3 × 10 mL). The collected ethereal phases were dried over Na_2SO_4 and concentrated to leave a yellowish oil. Treatment with 1 N HCl (6 mL) at 25 °C for 2 h, addition of NaOH until pH 11, extraction with Et_2O (3 × 5 mL), drying (Na_2SO_4) and evaporation of the solvent gave a yellow thick oil. The diastereomeric ratios were determined by GC-MS and 1H NMR analyses: **25a** 75:25, **25b** 85:15, **25c** 90:10. The major diastereomers of **25a-c** were separated by column chromatography (SiO_2; hexane/ethyl acetate with increasing polarity) with d.r. >95:5 and were used as such in the subsequent step. For analytical purpose, the pure diastereomers were obtained by repeated chromatography with slightly decreased yield. No attempt was made to isolate the minor diastereomers of **25a-c**. The minor diastereomers were not isolated in a pure state by column chropmatography.

***N*-[1(S)-(2-Quinolyl)-2-methylpropyl]-(*S*)-valinol (25a)**: Yellowish oil; 0.215 g (25%). $[\alpha]_D^{20}$ –70.7 (c 1.05, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 5.4 and 8.0 Hz, Ar), 7.80 (dd, *J* = 1.2 and 8.0 Hz, 1 H, Ar). 7.70 (m, 1 H, Ar), 7.51 (m, 1 H, Ar), 7.31 (d, *J* = 8.4 Hz, 1

H, Ar), 3.70 (dd, *J* = 3.6 and 10.6 Hz, 1 H, CH_2O), 3.61 (d, *J* = 6.6 Hz, 1 H, ArC*H*N), 3.45 (dd, *J* = 3.8 and 10.8 Hz, 1 H, CH_2OH), 2.5 (broad, 2 H, OH and NH), 2.13 (m, 1 H, CHN), 2.06 (m, 1 H, C*H*Me_2), 1.32 (s, 1 H, NH), 1.65 (m, 1 H, C*H*Me_2), 1.04 (d, *J* = 6.6 Hz, 3 H, CH*Me*), 0.86, 0.84 and 0.77 (3 d, *J* = 7.0 Hz, 9 H, CH*Me*$_2$). GC-MS *m*/*z* (relative intensity): 243 (100, $M^{+\cdot}$ *i*Pr), 184 (98), 142 (51), 199 (50), 154 (30), 158 (28), 157 (20), 169 (19), 170 (18), 255 (10, $M^{+\cdot}$ CH2OH). Found: C 75.55, H 9.18, N 9.70%; $C_{18}H_{26}N_2O$ requires: C 75.48; H 9.15, N 9.78%.

***N*-[1(*S*)-(8-Quinolyl)-2-methylpropyl]-(*S*)-valinol (25b)**: Yellowish oil; 0.325 g (1.14 mmol, 38%). $[\alpha]_D^{20}$ –49.1 (c 1.05, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.87 (dd, *J* = 1.8 and 4.4 Hz, Ar), 8.16 (dd, *J* = 1.8 and 8.4 Hz, 1 H, Ar), 7.72 (m, 1 H, Ar), 7.47 (d, *J* = 5.2 Hz, 2 H, Ar), 7.39 (dd, *J* = 4.4 and 8.0 Hz, 1 H, Ar), 3.95 (broad, 1 H, OH), 3.71 (dd, *J* = 4.0 and 10.6 Hz, 1 H, CH_2O), 3.43 (dd, *J* = 1.8 and 10.6 Hz, 1 H, CH_2O), 2.55 (m, 2 H, ArC*H*N and NH), 1.99 (m, 1 H, C*H*Me_2), 1.55 (m, 1 H, C*H*Me_2), 1.24 (d, *J* = 6.6 Hz, 3 H, CH*Me*), 0.64, 0.59 and 0.56 (3 d, *J* = 6.6 Hz, 9 H, CH*Me*$_2$). GC-MS *m*/*z* (relative intensity): 243 (100, M^+ – *i*Pr), 184 (98), 142 (51), 199 (51), 158 (28), 154 (26), 157 (20), 167 (19), 168 (18). Found: C 75.34, H 9.17, N 9.72%; $C_{18}H_{26}N_2O$ requires: C 75.48; H 9.15, N 9.78%.

***N*-[1(*S*)-(6-Benzyl-2-pyridyl)-2-methylpropyl]-(*S*)-valinol (25c)**: Yellowish oil; 0.546 g (56%). $[\alpha]_D^{20}$ –64.4 (c 0.68, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49 (t, *J* = 7.6 Hz, 1 H, Py), 7.36-7.14 (m, 5 H, Ph), 6.94 (t, *J* = 7.6 Hz, 2 H, Py), 4.14 (s, 2 H, C*H*$_2$Ph), 3.60 and 3.41 (2 dd, *J* = 3.8 and 10.8 Hz, 2 H, CH_2O), 3.30 (d, *J* = 7.4 Hz, 1 H, ArC*H*N), 2.15 (m, 1 H, NC*H*CH_2), 1.96 and 1.56 (2 m, 2 H, C*H*Me_2), 1.42 (broad, 2 H, NH and OH), 1.04, 0.77, 0.75 and 0.74 (4 d, *J* = 7.0 Hz, 12 H, CH*Me*$_2$). Found: C 77.33, H 9.32, N 8.52%; $C_{21}H_{30}N_2O$ requires: C 77.25; H 9.26, N 8.58%. The product decomposed during the GC-MS analysis.

Preparation of aziridines

1-[1(*R*)-(2-Pyridyl)-2-methylpropyl]-2(*R*)-phenylaziridine (21): Triethylamine (0.755 g, 7.4 mmol) and methanesulfonyl chloride (0.493 g, 4,44 mmol) were added to the solution of the diastereomerically pure aminoalcohol **17** (0.400 g, 1.48 mmol) in CH_2Cl_2 (12 mL) cooled at –78 °C and the mixture was stirred for 3 h. After quenching with sat. $NaHCO_3$ (5 mL), the organic layer was separated and the organic bases were extracted from the aqueous layer with CH_2Cl_2 (3 × 5 mL). The collected organic layers were dried ($CaCl_2$) and concentrated to leave an oil, which was chromatographed on a SiO_2 column eluting with

cyclohexane-ethyl acetate mixture, to obtain the compound **21** as a yellowish oil: 0.202 g, (55%). $[\alpha]_D^{20}$ −129.6 (c 0.44, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.5 Hz, 1 H, Py), 7.56 (dt, *J* = 1.5 and 7.5 Hz, 1 H, Py), 7.42 (d, *J* = 7.5 Hz, 1 H, Py), 7.35-7.0 (m, 6 H, Ar), 2.71 (d, *J* = 6.0 Hz, 1 H, NC*H*Py), 2.35 (dd, *J* = 3.3 and 6.5 Hz, PhC*H*CH_2), 2.28 (m, 1 H, C*H*Me_2), 2.16 (d, *J* = 3.3 Hz, 1.H, CHC*H*$_2$), 2.02 (d, *J* = 6.5 Hz, 1 H, CHC*H*$_2$), 1.10 and 0.97 (2 d, *J* = 6.6 Hx, 6 H, CH*Me*$_2$). GC-MS *m*/*z* (relative intensity): 118 (100, $PhCHCH_2N$), 91 (86), 136 (21), 119 (8), 78 (6), 182 (5), 104 (5), 209 (4, $M^{+\tilde{}}$ - *i*Pr). Found: C 80.97, H 8.04, N 11.05%; $C_{17}H_{20}N_2$ requires: C 80.91; H 7.99, N 11.10%.

Preparation of the aziridines 26a-c

The solution of 1,2-aminoalcohol (3 mmol) and 1,1'-carbonyldiimidazole (0.540 g, 3.3 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1.5 h, then the solvent was evaporated and the yellow-brown residue was dissolved in a 1:3 THF-H_2O mixture (80 mL). The mixture was vigorously stirred overnight, then THF was evaporated at reduced pressure and the organic phase was extracted with Et_2O (3 × 30 mL). The collected organic phases were dried (Na_2SO_4), then evaporated to leave an oily residue, which was chromatographed on a SiO_2 column, eluting with cyclohexane-ethyl acetate mixtures.

1-[1(*S*)-(2-Quinolyl)-2-methylpropyl]-2(*S*)-isopropylaziridine (26a): Yellowish oil; 0.507 g (63%), d.r. 95:5 (GC/MS). $[\alpha]_D^{20}$ −32.6 (c 1.05, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (dd, *J* 8.8 and 15.8 Hz, 1 H, Ar), 7.82 (d, *J* = 8.0 Hz, 1 H, Ar), 7.71 (t, *J* Hz, 2 H, Ar), 7.53 (t, *J* = Hz, 1 H, Ar), 2.41 (m, 2 H, NCH_2), 1.81 (t, *J* = Hz, 2 H, C*H*Me_2), 1.64 (d, *J* = 5.8 Hz, 1 H, ArC*H*N), 1.21 (d, *J* = 5.6 Hz, 3 H, ArCHCH*Me*$_2$), 1.15 (m, 1 H, NC*H*CH_2), 0.74 (t, *J* Hz, 6 H, CH*Me*$_2$), 0.35 (d, *J* = 6.4 Hz, 3 H, ArCHCH*Me*). GC-MS *m*/*z* (relative intensity): 155 (100), 197 (60), 142 (50), 168 (22), 225 (18, M^+ – *i*Pr). Found: C 80.59, H 9.06, N 10.42%; $C_{18}H_{24}N_2$ requires: C 80.55; H 9.01, N 10.40%.

1-[1(*S*)-(8-Quinolyl)-2-methylpropyl]-2(*S*)-isopropylaziridine (26b): Yellowish oil; 0.523 g (65%), d.r. 96:4 (GC/MS). $[\alpha]_D^{20}$ +15.7 (c 0.53, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 8.89 (m, 1 H, Ar), 8.15 (d, *J* = 8.1 Hz, 1 H, Ar), 8.05 (d, *J* = 6.4 Hz, 1 H, Ar), 7.70 (d, *J* = 8.1 Hz, 1 H, Ar), 7.60 (m, 1 H, Ar), 7.38 (m, 1 H, Ar), 3.86 (d, *J* 8.7 Hz, 1 H, ArCHN), 2.38 (m, 1 H, NC*H*CH_2), 1.80 (m, 2 H, NCHC*H*$_2$), 1.22 (d, *J* = 6.6 Hz, 3 H, CH*Me*), 1.03 (m, 2 H, C*H*Me_2), 0.67 and 0.66 (2 d, *J* = 6.6 Hz, 6 H, CH*Me*$_2$), 0.26 (d, *J* = 6.6 Hz, 3 H, CH*Me*). GC-MS *m*/*z*

(relative intensity): 155 (100), 197 (60), 142 (50), 225 (18), 168 (15), 184 (13), 268 (M^+, 10), 253 (5). Found: C 80.61, H 9.03, N 10.42%; $C_{18}H_{24}N_2$ requires: C 80.55; H 9.01, N 10.44%.

1-[1(*S*)-(6-Benzyl-2-pyridyl)-2-methylpropyl]-2(*S*)-isopropylaziridine (26c): Yellowish oil; 0.545 g (59%), d.r. 98:2 (GC/MS). $[\alpha]_D^{20}$ –44.5 (c 0.63, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.8 Hz, 1 H, 7.35-7-13 (m, 6 H, Ar), 6.93 (d, *J* = 7.8 Hz, 1 H, Py), 4.14 (s, 2 H, C*H*$_2$Ph), 2.28 (m, 1 H, C*H*CH$_2$), 2.18, d, *J* = 8.8 Hz, 1 H, NC*H*Ar), 1.77 (d, *J* = 3.6 Hz, 1 H, CHC*H*2), 1.54 (d, *J* = 6.2, 1 H, CHC*H*$_2$), 1.20 and 1.05 (2 m, 2 H, C*H*Me$_2$), 1.14, 0.74, 0.69 and 0.34 (4 d, *J* = 6.6 Hz, 12 H, CH*Me*$_2$). GC-MS *m/z* (relative intensity): 225 (100), 265 (88), 210 (58), 84 (47), 236 (35), 197 (33), 91 (20), 55 (17), 182 (16), 167 (13). Found: C 81.83, H 9.18, N 9.04; $C_{21}H_{28}N_2$ requires: C 81.77; H 9.15, N 9.08%.

Preparation of [(*N*,*N*')*(η^3-allylic)Pd][SbF_6] complexes

Allylpalladium chloride dimer (0.157 g, 0.43 mmol) was added to the solution of aziridine (0.86 mmol) in CH_2Cl_2 (15 mL). After stirring during 1 h, the solution became green, then a solution of silver hexafluoroantimonate (0.300 g, 0.86 mmol) in THF (6 mL) was added and the mixture was stirred for 30 min, during which time a white precipitate was formed. The solid was filtered off through a small pad of celite. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to leave a solid residue, which was then crystallised. The complex **12** has been previously described.[8]

Complex 22: Colourless crystals (CH_2Cl_2-Et_2O), 57% yield; m.p. 213-214 °C (dec.). $[\alpha]_D^{20}$ –31.6 (c 0.4, $CHCl_3$). The ^{1}H NMR (300 MHz, $CDCl_3$) showed the presence of two rotamers in 60:40 ratio (the absorptions of the prevalent rotamer are reported in bold character): δ **8.58** and 8.46 (2 d, *J* = 5.6 Hz, 1 H, Ar), 8.08 (m, 1 H, Ar), 7.77 (m, 1 H, Ar), **7.52** (m, 1 H, Ar), 7.47 (m, 1 H, Ar), 7.30 (m, 4 H, Ar), **7.10** (m, 1 H, Ar), 6.96 (m, 1 H, Ar), **5.53** and 4.55 (m, 1 H, CH_2CHCH_2), **3.93** and 3.73 (2 d, *J* = 6.6 Hz, 1 H, CH_2CHCH_2), 3.68 and **3.59** (2 d, *J* = 6.6 Hz, 1 H, PyC*H*), **3.58** and 3.26 (2 d, *J* = 6.6 Hx, 1 H, CH_2CHCH_2), **3.50** and 3.38 (2 dd, *J* = 7.3 and 5.0 Hz, 1 H, NC*H*CH_2), 3.11 and **3.0** (2 m, 2 H, NCHC*H*$_2$), 2.85 and **2.56** (2 d, *J* = 12.6 Hz, 1 H, CH_2CHCH_2), 2.55 and **2.27** (2 m, 1 H, C*H*Me$_2$), 1.44 (d, *J* = 12.6 Hz, 1 H, CH_2CHCH_2), 1.23, **1.16**, 1.09 and **0.87** (4 d, *J* = 6.8 Hz, CH*Me*$_2$).

Complex 28: Orange crystals (MeOH), 72% yield; m.p. 225-227 °C (dec.). $[\alpha]_D^{20}$ +26.5 (c 0.58, $CHCl_3$). IR (KBr) 2980, 1607, 1533, 1490, 1474, 1446, 1388, 1159, 1015, 758, 698 cm^{-1}. The ^{1}H NMR (200 MHz, $CDCl_3$) showed the presence of two rotamers in 70:30 ratio

(the absorptions of the prevalent rotamer are reported in bold character): δ 7.95 (t, *J* = 6.6 Hz, 1 H, Ar), 7.80-6.95 (m, 17 H, Ar), 6.50 and **6.31** (2 d, *J* = 5.2 and 7.4 Hz, 1 H, Ar), **6.25** and 5.67 (2 dd, *J* = **11.0** and **11.4**, 12.4 and 10.6 Hz, 1 H, CHC*H*CH), 5.03 and **3.82** (2 d, *J* = 12.4 and **11.4** Hz, 1 H, C*H*CHCH), 4.47 and **2.82** (2 d, *J* = 10.6 and **11.0** Hz, 1 H, C*H*CHCH), 3.73 and **3.37** (d, *J* = 6.8 and **7.2** Hz,1 H, C*H*Py), 3.33 and 2.90 (2 m, 2 H, NCHCH_2), 2.83 and **2.11** (m, 1 H, C*H*Me_2), 2.43 and **2.27** (2 dd, *J* = 2.2, 8.0 Hz, **2.2** and **7.4** Hz, 1 H, NC*H*CH_2), 1.34, 1.0, **0.96** and **0.86** (4 d, *J* = 6.6 and **7.0** Hz, 6 H, CH*Me*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (major diastereomer) = 159.7, 149.0, 139.2, 136.2, 136.1, 132-126 (m), 125.0, 124.7, 106.0, 81.4, 75.8, 45.2, 34.85, 20.1, 18.8. Found: C 48.68, H 4.40, N 3.48; C32H33F6N2PdSb requires: C 48.79; H 4.22, N 3.56%.

Complex 27a: Colourless crystals (CH_2Cl_2-Et_2O), 70% yield; m.p. 182-185 °C (dec.). $[\alpha]_D^{20}$ +101.1 (c 1.06, $CHCl_3$). The ^{1}H NMR (300 MHz, $CDCl_3$) showed the presence of two rotamers in 65:35 ratio (the absorptions of the prevalent rotamer are reported in bold character): δ = 8.50 (2 d, *J* = 8 Hz, 1 H, Ar), 8.18-7.88 (m, 3 H, Ar), 7.70 (m, 2 H, Ar), 5.88 and **5.75** (2 m, 1 H, CH2C*H*CH2), 4.79 and **4.50** (2 d, *J* = 7.2 and 7.2 Hz, 1 H, C*H*2CHCH2), **4.13** and 3.95 (2 d, *J* = **6.6** and 7.2 Hz, 1 H, C*H*2CHCH2), 3.53 and **3.43** (2 d, *J* = 7.8 Hz, 1 H, ArC*H*), **3.45**, 3.38, 3.32 and **3.16** (4 d, *J* = 12.6 Hz, 2 H, C*H*2CHCH2), 2.82 and **2.49** (2 m, 1 H, NC*H*CH_2), 2.75 and 2.40 (2 m, 2 H, NCHCH_2), **1.92** and 1.86 (2 m, 1 H, C*H*Me_2), 1.41, **1.28**, 1.10, **1.00**, **0.93**, 0.91, **0.74** and 0.51 (8 d, *J* = 6.6 Hz, 12 H, CH*Me*$_2$).

Complex 27b: Colourless crystals ($CHCl_3$), 79% yield; m.p. 215-218 °C (dec.). [¤]$_D^{20}$ +54.5 (c 0.58, $CHCl_3$). The ^{1}H NMR spectrum (200 MHz, CD_2Cl_2) showed the presence of two rotamers in 55:45 ratio (the absorptions of the prevalent rotamer are reported in bold character): δ = **9.29** and 9.21 (2 d, *J* = 5.0 Hz, 1 H, Ar), 8.51 (t, *J* = 8.7 Hz, 1 H, Ar), 7.99 (d, *J* = 5.7 Hz, 1 H, Ar), 7.63 (m, 3 H, Ar), 6.12 (m, 1 H, CH_2C*H*CH_2), **4.12** and 4.01 (2 d, *J* = **7.4** and 5.8, 1 H, C$H_2$$CHCH_2$), 3.76 (m, 1 H, C$H_2$$CHCH_2$), 3.53 (d, *J* = 7.0 Hz, 1 H, ArC*H*), **3.43** and 3.31 (2 d, *J* = **12.2** and 12.4 Hz, 1 H, C$H_2$$CHCH_2$), 3.10 (m, 1 H, NC*H*CH2), **3.09** and 3.67 (2 d, *J* = **11.8** and 10.4 Hz, 1 H, C$H_2$$CHCH_2$), 2.55 and 2.42 (2 m, 2 H, NCHCH_2), 1.61 and 1.25 (2 m, 2 H, C*H*Me_2), 1.50, **1.33**, **0.91**, 0.84, 0.61, **0.57**, **0.20**, 0.07 (8 d, *J* = 6.6 Hz, 12 H, CH*Me*$_2$).

Complex 27c: Colourless crystals (MeOH), 61% yield; m.p. 223-224 °C (dec.). $[\alpha]_D^{20}$ +4.2 (c 1.0, $CHCl_3$). The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) showed the presence of two rotamers in 55:45 ratio (the absorptions of the prevalent rotamer are reported in bold character): δ 7.85 (2 t, *J* = 7.8 Hz, 1 H, Py), 7.53-7.28 (m, 4 H, Ar), 7.15 (m (3 H, Ar), 5.72 (m, 1 H, CH_2C*H*CH_2), **4.36** and 4.27 (2 s, 2 H, CH_2Ph), 4.35 and 4.28 (2 d, *J* = 6.6 Hz, 1 H,

C*H*$_2$CHCH$_2$), **4.06** and 3.89 (2 d, *J* = 6.6 Hz, 1 H, C*H*$_2$CHCH$_2$), 3.34, 3.22, 3.14 and 3.10 (4 d, *J* = 12.4 Hz, 2 H, 2 C*H*$_2$CHC*H*$_2$), 3.24 and 3.13 (2 d, *J* = 8.2 Hz, 1 H, NC*H*Ar), 2.84 and **2.50** (2 m, 1 H, NC*H*CH$_2$), 2.68 and **2.38** (2 m, 2 H, CHC*H*$_2$), 1.88, 1.81, 1.45 and 1.18 (4 m, 2 H, C*H*Me$_2$), 1.37, **1.25**, 1.05, 1.03, 0.94, **0.90**, **0.89** and 0.65 (8 d, *J* = 6.7 Hz, 12 H, CH*Me*$_2$).

Complex 29: Orange crystals (MeOH), 77% yield; m.p. 218-219 °C (dec.). $[\alpha]_D^{20}$ +84.9 (c 0.68, $CHCl_3$). IR (KBr) 2950, 1607, 1570, 1540, 1491, 1464, 1023, 889, 756, 697 cm^{-1}. The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) showed the presence of two rotamers in 85:15 ratio (the absorptions of the prevalent rotamer are reported in bold character): δ 7.80-7.10 (m, 16 H, Ar), 6.90-6.60 (m, 2 H, Ar), 6.55 and **6.44** (2 dd, *J* = 11.2 and **11.4** Hz, 1 H, CHC*H*CH), 5.33 and **4.86** (2 d, *J* = 10.8 Hz, 1 H, C*H*CHCH), 4.78 and **4.72** (d, *J* = 12.0 Hz, 1 H, C*H*CHCH), **4.29**, **3.75,** 3.21 and 3.01 (4 d, *J* = **17.0** and 14.0 Hz, 2 H, CH_2Ph), **2.91** (d, *J* = 8.7 Hz, 1 H, NC*H*Py), 2.72 (m, 1 H, NC*H*CH$_2$), 1.60-1.40 (m, 4 H, 2 C*H*Me$_2$ and NCHC*H*$_2$), **1.14**, 1.02, **0.91**, **0.89**, **0.87**, 0.55. 0.50 and 0.40 (8 d, *J* = 6.6 Hz, CH*Me*$_2$). ^{13}C NMR of the major diastereomer (75 MHz, DMSO-d_6): δ = 162.1, 160.5, 139.8, 137.2, 136.1, 132-128, 123.8, 122.6, 107.9, 81.8, 80.0, 76.9, 45.9, 35.9, 33.1, 21.1, 21.0, 20.0, 19.6. Found: C 51.35, H 5.02, N 3.42; $C_{36}H_{41}F_6N_2PdSb$ requires: C 51.24, H 4.90, N 3.32%.

(*E*)-1,3-Diphenyl-2-propen-1-yl ethyl carbonate: Ethyl chloroformate (1.84 g, 17 mmol) was slowly added to the stirred solution of 1.3-diphenyl-2-propen-1-ol (1.05 g, 5 mmol), pyridine (1.5 g, 19 mmol), and 4-dimethylaminopyridine (10 mg) in THF (10 mL) at 0 °C. The mixture was stirred at 20 °C for 48 h, after which time H_2O was added and the organic phase extracted with Et_2O (3 × 10 mL). The collected organic layers were washed with 1 N HCl (10 mL), with sat. $NaHCO_3$ and brine, then dried (Na2SO4) and concentrated to leave **1b** in almost quantitative yield. The compound decomposed during GC analysis, but a purity >95% was determined by ^{1}H NMR analysis and was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60-7.20 (m, 10 H, Ph), 6.82 (d, *J* = 15.4 Hz, 1 H, PhC*H*=CH), 6.42 (d, *J* = 8.4 Hz, 1 H, C*H*O), 6.27 (dd, *J* = 15.4 and 8.4 Hz, 1 H, PhCH=C*H*CHPh), 4.21 (dq, *J* = 1.0 and 6.2 Hz, CH_2O), 1.31 (t, *J* = 6.2 Hz, 3H, CH_3).

Palladium-catalysed allylic substitution reactions. Preparation of (*S*)-2.

The palladium salt **22** (0.061 g, 0.1 mmol) was added to a stirred solution of 1,3-diphenyl-2-propenyl ethyl carbonate **1b** (0.28 g, 1 mmol) in THF (5 mL) under Ar at room temperature. Then, a solution of sodium dimethyl malonate, generated from dimethyl

malonate (0.198 g, 1.5 mmol) and NaH (0.036 g, 1.5 mmol) in THF 6 mL), was added dropwise and the mixture was magnetically stirred overnight. 1 N HCl (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL), the organic phase was dried (Na_2SO_4) and evaporated. Chromatography of the residue on a SiO_2 column eluting with cyclohexane-ethyl acetate (15:1) gave the product (*S*)-**2**: 0.227 g (70%); $[\alpha]_D^{25}$ −15.4 (c 0.42, EtOH); the e.e. 90% was determined by HPLC analysis (Daicel Chiralcel™ OD column, *n*-hexane/*i*PrOH 99:1, flow rate 0.5 mL/min, the product was eluted at 21.15 (*R* enantiomer) and 22.22 min (*S* enantiomer).

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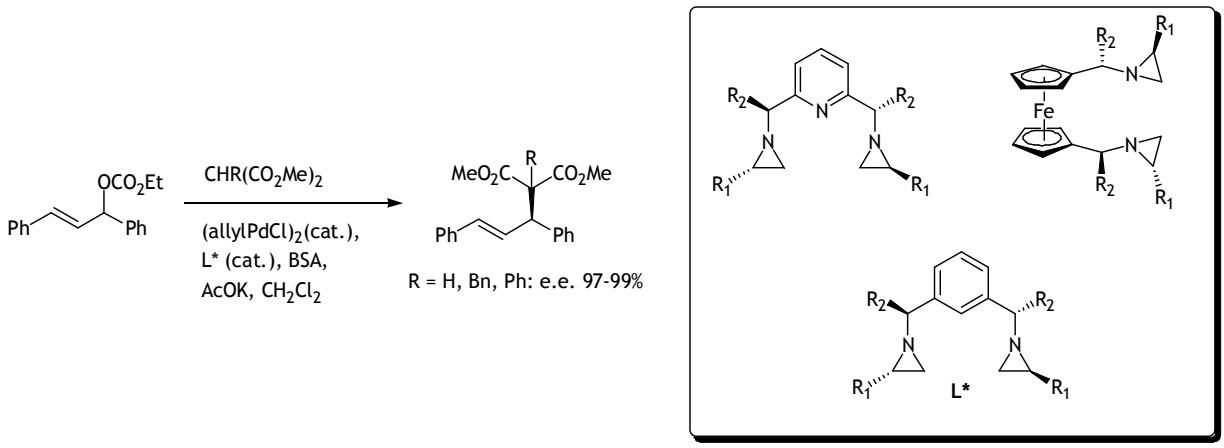
Chapter 6

New chiral ligands featuring two aziridine rings separated by an aromatic spacer. Synthesis and applications.



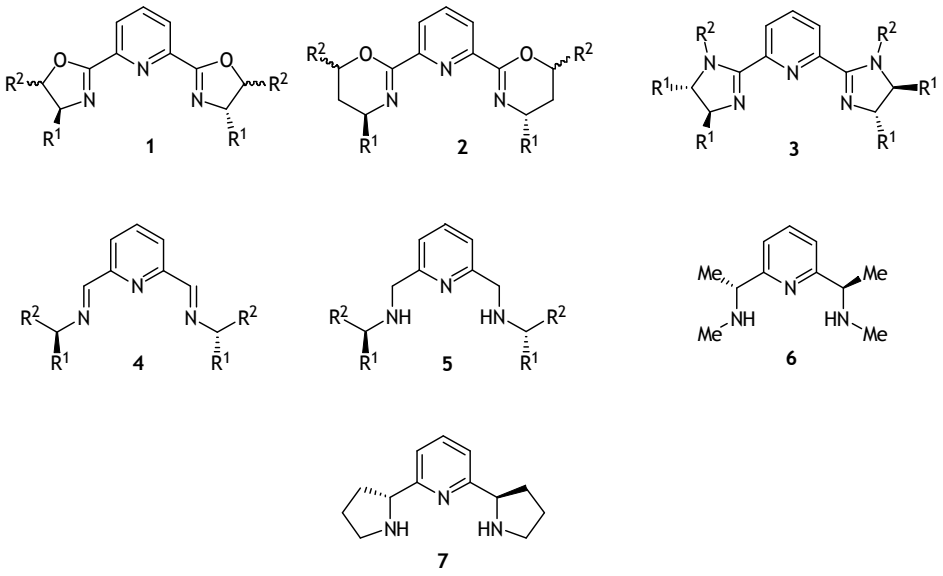
6.1. Introduction

Nitrogen-containing ligands are increasingly being applied in asymmetric catalysis,[1] since they present several advantages with respect to the more conventional phosphorus-containing ligands, even in transition metal-catalyzed reactions, since the amine functionality can coordinate any metal species, ranging from lithium and magnesium to zinc, copper, early transition metal complexes and also precious metals.

A significant niche in the domain of nitrogen ligands is hold by N,N',N"-terdentate ligands, especially those having C_2-symmetry. The pyridine ring is present in most compounds of this type, where it has the role of a spacer between two identical N-containing moieties as in the widely used and highly performing pyridine-bis(oxazolines) **1** (Pybox's)[2] and the more recently developed pyridine-bis(oxazines) (Pyboxazines) ligands **2**[3] and pyridine-bis(imidazolidines) **3**.[4] Both ligands **1** and **2** are readily prepared from 2,6-pyridinedicarboxylic acids and enantiopure β- and γ-aminoalcohols, respectively, without need to construct new stereocenters.

Pyridinediimines **4**, which are similarly prepared from 2,6-pyridinedicarbaldehyde, have been also used as ligands in metal-catalyzed asymmetric reactions.[5] Moreover, N,N',N"-terdentate ligands **5**[6] bearing two chiral amine functions in the lateral chains of the pyridine ring were prepared from 2,6-di(chloromethyl)pyridine, then used in transamination reactions with moderate enantioselectivities. However, only a few

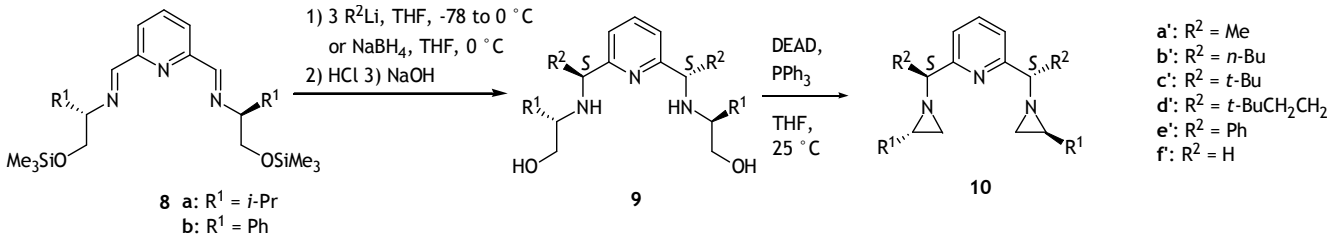
compounds with stereocenters at the benzylic positions have been described. The (*R*,*R*)- and (*S*,*S*)-enantiomers of the ligands **6**[6a] and **7**[7] were obtained after separation from the *meso*-compounds and resolution of the racemic mixture or copper complex, but no application of these ligands in asymmetric syntheses has been until now described. Also, chiral C_2-symmetric substituted bipyridines and terpyridines have been exploited as metal ligands for asymmetric synthesis.[1c]



As an evolution of the chiral pyridine-aziridine chiral ligands we described in the previous chapter, we envisioned a similar three step route to enantiopure C_2-symmetrical N,N',N"-terdentate ligands involving the addition of organometallic reagents to a chiral diimine derived from 2,6-pyridinedicarbaldehyde **8a** and **8b** and (*S*)-valinol and (*S*)-phenylglycinol, respectively. As a matter of fact, preliminary experiments showed that Grignard reagents were poorly effective. While the reactions with allylic zinc reagents have been described in chapter 4, best results were obtained with organolithium compounds, then the conversion of the β-aminoalcohol products **9** to 2,6-**di**[1-(1-**az**iridinyl)**a**lkyl]**p**yridines (DIAZAP's) **10** was achieved by a Mitsunobu reaction. By this strategy, the carbon skeleton of the starting chiral aminoalcohol and the absolute configuration of the inherent stereocenters are retained in the final molecule. The new ligands were then used in palladium catalyzed asymmetric allylic alkylation (AAA) of stabilized carbanions, providing higher enantioselectivity with respect to the analogous, previously described, bidentate pyridine-aziridine ligands.[8]

6.2. Preparation of the DIAZAP ligands

The starting *O*-silylated diimines **8a** and **8b** were prepared in almost quantitative yields from the corresponding diimines bearing unprotected OH groups by the protocol previously described for the analogous monoimines, [8][9] and then used directly in the following step without purification. As stated before, Grignard reagents were not effective and led generally to mixture of products coming from the further attack to the pyridine moiety. Organolithium compounds were found to be the reagents of choice to achieve a highly efficient, regio- and diastereoselective double addition to the azomethine groups in anhydrous tetrahydrofuran (THF) at -78 °C under an inert atmosphere. 3,3-Dimethylbutyllithium was prepared by the reaction of *t*-butyllithium (2 equivalents) with THF (solvent) at room temperature, involving the addition of *t*-butyllithium to ethylene, which is formed together with the lithium enolate of acetaldehyde following the initial cleavage of THF by *t*-butyllithium.[10] It is noteworthy that almost all the reactions gave the expected products **9a** and **9b** in high yields and with very high diastereoselectivities. As a matter of fact, apart from the addition of *t*-butyllithium to both imines (entries 3 and 8), which provided the corresponding aminoalcohols with low diastereomeric ratios, the reactions of organolithium reagents with the valinol-derived imine **8a** occurred in most cases with higher diastereoselectivities (d.r. of **9a** 94:6) with respect to the phenylglycinol-derived imine **8b** (d.r. of **9b** 91:9). For the imine **8a**, the best result was obtained with phenyllithium, which afforded the aminoalcohol **9ae'** in 95% yield and d.r. 98:2. However, the addition of methyllithium to **8b** (entry 6) was even more diastereoselective, as the pure diastereomer (*S*,*S*)-**9ba'** was obtained in 94% yield after column chromatography of the crude reaction product, where no other diastereomer was detected by ^{1}H NMR spectroscopy.



8 a: R^1 = *i*-Pr
b: R^1 = Ph

9

10

Entry	Imine (R1)	R_2Li	Product	D.r.[a]	9, Yield %[b]	10, Yield %[c]
1	**8a** (*i*-Pr)	MeLi	**9aa'**	95:5	95	**10aa'** (85)
2	"	*n*-BuLi	**9ab'**	95:5	95 (79)[c]	**10ab'** (87)

3	"	*t*-BuLi[d]	**9ac'**	84:16	95 (54)[c]	**10ac'** (84)[e]
4	"	*t*-$BuCH_2CH_2Li$[f]	**9ad'**	94:6	84 (70)[c]	**10ad'** (86)
5	"	PhLi	**9ae'**	98:2	95	**10ae'** (90)
6	**8b** (Ph)	MeLi	**9ba'**	>99:1	94[g]	**10ba'** (85)
7	"	*n*-BuLi	**9bb'**	91:9	93 (76)	**10bb'** (90)[h]
8	"	*t*-Bu[d]	**9bc'**	86:14	94(59)	**10bc'** (86)[i]
9	"	PhLi	**9be'**	92:8	98 (84)	**10be'** (89)[j]

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction products. [b] Yield of the crude reaction product. Unless otherwise indicated, the diastereomers were not separated. [c] Yield of pure (*S*,*S*)-**9** isolated after column chromatography. [d] The reaction was performed in diethyl ether. [e] The product was obtained after column chromatography as a 89:11 mixture of diastereomers. [f] The reagent was prepared in situ by adding *t*-BuLi to THF (solvent) at 0 °C. [g] The crude product was apparently pure by ^{1}H NMR spectroscopy. [h] The product was obtained after column chromatography as a 91:9 mixture of diastereomers. [i] The product was obtained after column chromatography as a 86:14 mixture od diastereomer. [j] The product was obtained after column chromatography as a a 92:8 mixture of diastereomers

It should be observed that all the organometallic additions produced only two of three possible diastereomers of the compounds **9**: the prevalent one had C_2-symmetry, as observed by ^{1}H NMR spectroscopy. The *S*,*S* configuration of the two newly formed stereocenters at the benzylic positions was at first assumed considering the sense of asymmetric induction previously observed in the addition of organolithium reagents to the analogous 2-pyridine monoamine,[8][9] and was then confirmed by the X-ray structure obtained for one palladium complex derived from one of these ligands (see later). Column chromatography of the crude reaction products often allowed isolation of the main diastereomer only, however, enriched chromatographic fractions of the minor diastereomer were obtained, allowing its C_1 symmetry to be determined. In particular, the separation of the diastereomers was difficult for **9aa'** and **9ac'**, and low yields of the pure main (*S*,*S*)-diastereomer were obtained. In these cases, it was preferable to merely filter the crude reaction mixtures through a small pad of silica and use the diastereomeric mixtures in the subsequent step, that is the cyclization to DIAZAP's **10aa'** and **10ac'**, since the diastereomers of the latter compounds were more readily separated by chromatography.

The reaction protocols that were successful for the construction of the mono-aziridine ligands here they did not give good results. Instead we found that the Mitsunobu reaction using (diethylazadicarboxylate (DEAD) and triphenylphosphine in THF at room temperature) gave much better results. DIAZAP's **10a** and **10b** were so obtained with high yields. In the

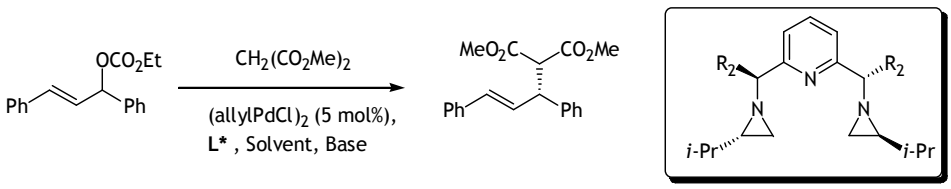
case of phenylglycinol derivatives, the diastereomers of the aminoalcohols **9bb'**, **9bc'** and **9be'** and the corresponding aziridines **10bb'**, **10bc'**and **10be'** could not be separated.

6.3. Pd-catalyzed AAA reactions in the presence of DIAZAP ligands

The major drawbacks of previously used bisdentate ligands (pyridine-aziridines) were their low reaction rates, even with the reactive 1,3-diphenylallyl carbonate **14b**, and their incapability to adequately stabilize zerovalent palladium emanating from the nucleophilic attack on the intermediate η^3-allylic complex, causing the precipitation of Pd black and consequently a low to moderate yield of product **15**. Hence, we designed the structure of the N,N',N"-terdentate DIAZAP ligands to overcome those problems. Our idea was also based on the report that a higher reaction rate was obtained using a P,N,N-terdentate ligand instead of a bidentate P,N-ligand in Pd-catalyzed AAA reactions;[11] a result that may have been the consequence of the capability of the terdentate ligand to effectively stabilize either Pd(0) or the (allylic)Pd(II)$^+$ complexes involved in the catalytic cycle. However, in the case of our terdentate ligands, taking into account the effects of substituents in the bidentate ligands on enantioselectivity, it was difficult to foresee the importance of the C6 pyridine substituent (aziridine-alkyl group) in **10**, which could potentially oppose the asymmetric induction of the aziridine substituent.

A number of reactions were carried out on the allylic carbonate **14b** with the anion of dimethyl malonate, generated by treatment of dimethylmalonate with either sodium hydride or bis(trimethylsilyl)amide (BSA) and a catalytic amount of potassium acetate in different solvents (Scheme 2 and Table 2). Allylpalladium chloride dimer and the terdentate ligands **10a** and **10b** were used as precursors of the effective enantioselective catalyst. The ligands derived from (*S*)-valinol were examined first. The carbonate **14b** was treated with the pre-formed sodium salt of dimethyl malonate (1.5 molar equivalents) and catalytic amounts of allylpalladium chloride dimer (5 mol%) and ligand **10aa'** (10 mol%) in tetrahydrofuran at room temperature. The course of the reaction was monitored by GC and TLC analysis and an almost complete conversion of the starting compounds was observed after 24 h. The product **15** was isolated in high yield and 76% e.e. in favour of the *R* enantiomer (Table 2, entry 1). It should be observed that the prior preparation of the palladium salt [(η^3-allyl)(**10aa'**)Pd][SbF_6] was unnecessary, as a smooth reaction occurred and the formation of black palladium was observed only when the reaction was almost complete. In a second run (entry 2) at -20 °C, with all the other experimental conditions

being unchanged, we observed that the same e.e. was obtained, but a longer reaction time was required to obtain a satisfactory yield of product. Hence, all the successive reactions were carried out at 25 °C.



Entry	Ligand (mol%)	Base	Solvent	Time (h)	Yield (%)	E.e. (%)
1	**10aa'** (10)	NaH	THF	24	79	76
2	**10aa'** (10) [b]	"	THF	96	69	76
3	**10aa'** (10)	"	CH_2Cl_2	48	85	73
4	**10ab'** (10)	"	THF	24	81	63
5	**10ab'** (10)	"	CH_2Cl_2	48	86	60
6	**10ac'** (10, d.r. 89:11)	BSA/AcOK	CH_2Cl_2	48	84	69
7	**10ad'** (10)	NaH	THF	48	86	70
8	**10ad'** (10)	BSA/AcOK	CH_2Cl_2	16	90	62
9	**10ae'** (10)	NaH	THF	24	85	76
10	**10ae'** (10)	NaH	CH_2Cl_2	18	89	86
11	**10ae'** (10)	BSA/AcOK	CH_2Cl_2	15	90	82
12	**10ae'** (10)	BSA/AcOLi	CH_2Cl_2	24	89	88
13	**10af'** (10)	BSA/AcOK	CH_2Cl_2	24	87	13

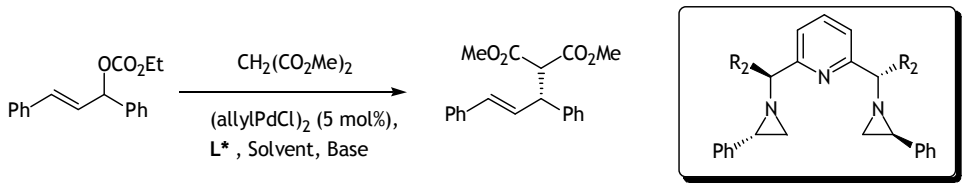
The role of the solvent was then examined and it was found that the reaction takes place also in dichloromethane, despite the poor solubility of sodium dimethyl malonate and the consequent lower reaction rate, but a slightly lower e.e. was obtained (entry 3). The same trend was observed when the *n*-butyl substituted ligand **10ab'** was used in both solvents, but the e.e.'s (60-63%) were lower (entries 4, 5). Similar results were obtained with the *t*-butyl substituted ligand **10ac'** (used as a 84:16 mixture of unseparable diastereomers) and the ligand **10ad'** (R^2 = *t*-BuCH_2CH_2) in different experimental conditions. Finally, the phenyl substituted ligand **10ae'** provided high levels of enantioselectivity with e.e. up to 88% in entry 12.

Again, we wanted to demonstrate the need of a substituent at the benzylic positions since this would induce the stereoselective formation of the N-aziridine stereocenter in the

cationic palladium complex. It should be observed that *N*-alkyl aziridines are not pyramidally stable at room temperature, and the bulkiness of the substituent decrease the barrier of inversion.[12] As demonstrated in the previous chapter, all the previously prepared η^3-allylic palladium complexes carrying bidentate (N,N)*-ligands displayed a unique configuration of the aziridine nitrogen atoms, that is dictated by the configuration of the benzylic carbon stereocenters and minimises the steric interactions between the benzylic (R^2) and aziridine (R^1) substituents. To that purpose, we synthesized the ligand **10af'** by reduction of the diimine **8a** to give the intermediate diaminediol **9a,f'**, followed by the usual cyclization step (Scheme 1). The correctness of our hypothesis was demonstrated by the observation that the typical allylic alkylation of sodium dimethyl malonate with the allylic carbonate **14a** in THF at 25 °C in the presence of 10 mol% of ligand **10af'** occurred with very low enantioselectivity (13% e.e., entry 13).

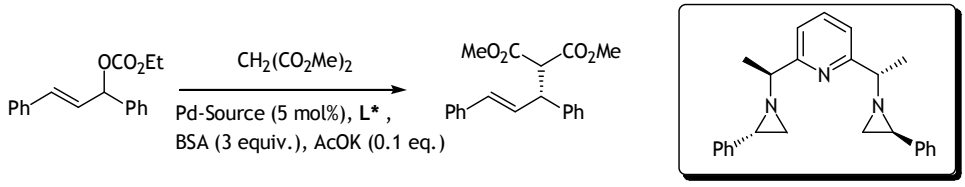
The terdentate ligands **10b**, derived from (*S*)-phenylglycinol and hence carrying phenyl substituents on the aziridine rings, were then examined in the same typical AAA reaction Table 3). (*R*)-**15** was formed in all cases with e.e.'s definitely superior to those obtained with the corresponding (*S*)-valinol-derived ligands **10a**. For example, using sodium hydride as the base in THF in the presence of allylpalladium chloride dimer (5 mol%) and the ligand **10ba'** (10 mol%) the product (*R*)-**15** was obtained with 82% yield and 82% e.e. after 72 h (entry 14). Then, we observed that in dichloromethane, despite the very low solubility of sodium dimethyl malonate, the reaction with the ligand **10ba'** was almost complete after only 3 h and the product was obtained with excellent yield and 98% e.e. (entry 15). The same level of enantioselectivity was obtained by performing the reaction with the same ligand and generating the nucleophile by the alternative protocol (BSA-AcOK in DCM, entry 16), even with reduced amounts of ligand (3 mol%, entries 17 and 18).

It was apparent that an increase in the bulkiness of the R^2 substituents in the ligands **10b** caused a decrease of the reaction rate. The *n*-butyl- and phenyl-substituted ligands **10bb'**, **10bc'** and **10be'** were used as an unseparable mixture of diastereomers, with the (*S*,*S*) and (*S*,*R*) configurations of the two benzylic stereocenters (d.r. 91:9, 86:14 and 92:8, respectively); nevertheless high e.e.'s were obtained (e.e.'s 80, 81, 70 and 83% in entries 19 to 22). Finally, we were surprised to find that the ligand **10bf'** (R^2 = H, Scheme 1), in contrast to the analogous (*S*)-valinol-derived **10af'** (13% e.e., entry 13), provided a moderate enantioselectivity (76% e.e., entry 23).



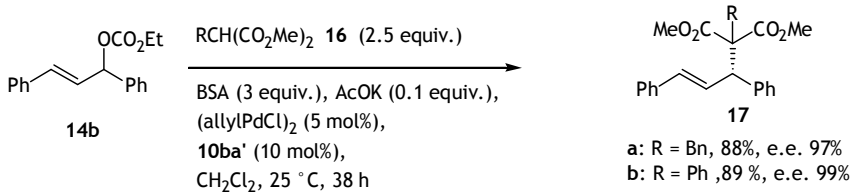
Entry	Ligand (mol%)	Base	Solvent	Time (h)	Yield (%)	E.e. (%)
14	**10ba'** (10)	NaH	THF	72	82	82
15	**10ba'** (10)	NaH	CH_2Cl_2	3	90	**98**
16	**10ba'** (10)	BSA/AcOK	CH_2Cl_2	2	92	**98**
17	**10ba'** (3)	BSA/AcOK	CH_2Cl_2	8	87	**98**
18	**10ba'** (3)	BSA/AcOLi	CH_2Cl_2	5	90	**98**
19	**10bb'** (10, d.r. 91:9)	NaH	THF	48	77	80
20	**10bb'** (10, d.r. 91:9)	BSA/AcOK	CH_2Cl_2	16	89	81
21	**10bc'** (10, d.r. 86:14)	BSA/AcOK	CH_2Cl_2	48	64	70
22	**10be'** (10, d.r. 92:8)	BSA/AcOK	CH_2Cl_2	16	88	83
23	**10bf'** (10)	BSA/AcOK	CH_2Cl_2	24	92	76

The role of different palladium sources was briefly investigated carrying out the allylation of the malonate anion (BSA, AcOK) with the carbonate **14b** in the presence of the ligand **10ba'** in dichloromethane at 25 °C. In comparison with the reaction catalyzed by allylpalladium chloride dimer (entry 1), which was almost complete after only 3 h, the reactions catalyzed by palladium acetate, palladium chloride and the dibenzylideneacetonate complex required 24 h to give comparable yields and slightly lower e.e.s; up to 85% yield and 96% e.e. were obtained with the latter catalyst (entry 4).

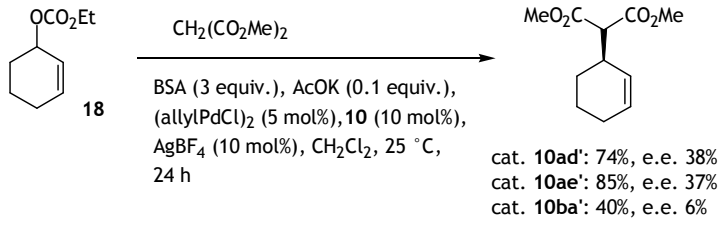


Entry	Pd catalyst (3 mol%)	Time (h)	Yield (%) of (*S*)-15	E.e. (%)
1	$(allylPdCl)_2$	3	87 [b]	98
2	$Pd(OAc)_2$	24	76	87
3	$PdCl_2$	24	81	94
4	$Pd(dba)_2CHCl_3$	24	85	96

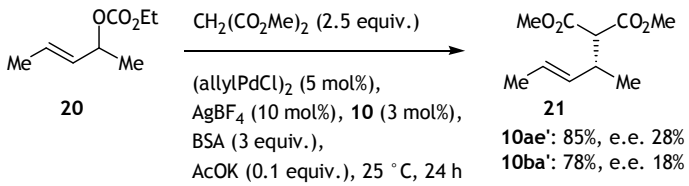
Then, to extend the scope of our catalytic system, we investigated the AAA reactions of other stabilized enolates as well as diversely substituted allylic carbonates (Scheme 3). The enolates derived from substituted malonates have been relatively less employed as nucleophiles, and chiral P,P, P,N and N,P,N ligands have been used.[13] We were pleased to find that the alkylations of the benzyl- and phenyl-substituted malonate esters **16a** and **16b**, respectively, proceeded smoothly in the presence of the ligand **10ba'** to give the products **17a** and **17b** in high yields and with 97-99% e.e.'s. The *S* configuration of the stereocenter in **17a** was assigned on the basis of the optical rotation (-)[13e] Since the previously unknown compound **17b** has the same sense of optical rotation of **17a**, the same configuration is assumed.



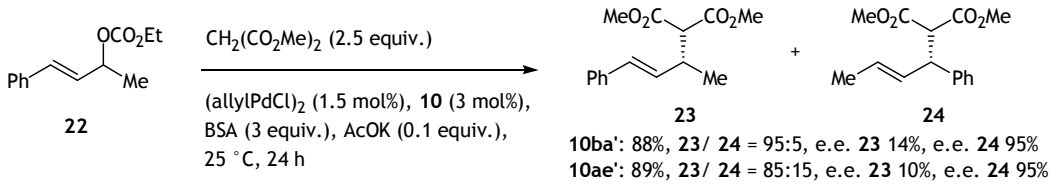
The cyclohexenyl carbonate **18** was poorly reactive in the usual experimental conditions and the e.e. of the derived product **19**[14] was low. For example, using ligand **10ba'**, a 40% yield and 6% e.e. were achieved, whereas a 68% yield and 37% e.e. were obtained with the ligand **10ae'**, in both cases after 3 days. The reaction rate could be slightly increased in the presence of silver tetrafluoroborate, and good yields of the cyclohexenyl-substituted malonate **19** were obtained after 2 days using either ligand **10ad'** or **10ae'**, but the e.e. did not exceed 38%. Surprisingly, the use of ligand **10ba'** resulted in a low yield of **19** (40%) and very low e.e. (6%).



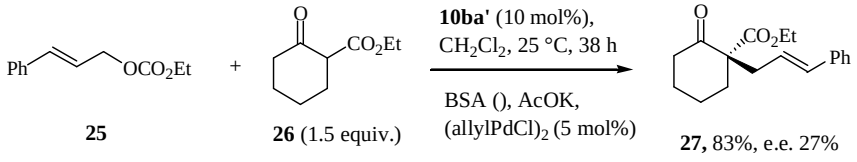
Similarly, the reaction of dimethyl malonate anion with ethyl 3-penten-2-yl carbonate **20** in the presence of the ligands **10ae'** and **10ba'** afforded the substitution product **21** in good yields in the presence of $AgBF_4$, but with low e.e.s (up to 28%).



Utilizing the unsymmetrically disubstituted allylic carbonate **22**, a mixture of products (ratio 95:5) was obtained, as usually found with other ligands:[15] the prevalent product **23** was formed by attack at the methyl-substituted allylic terminus with low enantioselectivity (e.e. 14%), whereas the minor regioisomer **24** was obtained with 95% e.e.

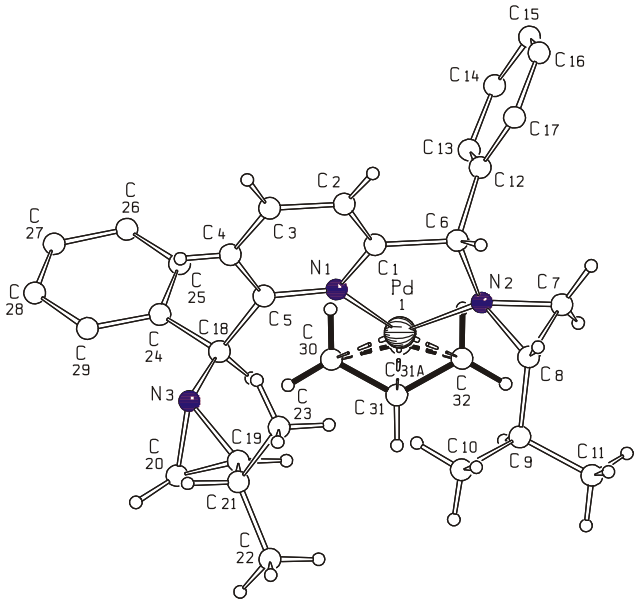


Finally, we turned our attention to the capability of our catalytic system to induce enantioselectivity in the formation of a quaternary stereogenic center at the nucleophilic carbon. This goal should be achieved by the discrimination of the two diastereotopic faces of a fully substituted planar enolate attacking the η3-allylic ligand. This is difficult to realise because the chiral N,N,N-ligand does not interfere in any way with the incoming nucleophile, and the newly formed stereocenter is more remote from the inducing stereocenter(s) than in previous experiments. Hence, we investigated the reaction of (*E*)-cinnamyl ethyl carbonate **25** with the anion derived from 2-ethoxycarbonylcyclohexanone **26** under the usual reaction conditions (BSA, AcOK, CH_2Cl_2). The reaction proceeded smoothly to give the linear alkylation product **27** with high yield but only 27% e.e.. This result can be compared with the reported Pd-catalyzed enantioselective synthesis of **27** using a P-chirogenic diaminophosphine oxide as the ligand, where 92% e.e. was obtained[16b] We assigned the *S* configuration to the major enantiomer of **27** by comparison with the authentic enantiomer.[16b]



6.3. Tentative explanation of mechanism and enantioselectivity

Different (allyl)- and (1,3-diphenylallyl)Pd+ salts bearing the (*S*)-valinol- and (*S*)-phenylglycinol-derived ligands, **10ae'** and **10ba'**, with PF_6, SbF6 or BF_4 counterions, were prepared by standard methodology. These salts were generally obtained as white or yellowish powders, and some of them appeared impure by ^{1}H NMR analysis. Up till now, we have succeeded to obtain crystals suitable for X-ray crystallographic structure determinations only in the case of the salt [(**10ae'**)(allyl)Pd][PF_6].



The crystal structure is quite similar to those of the previously reported allylic palladium salts with pyridine-aziridine ligands,[8] featuring the bidentate coordination of the ligand to palladium cation and the η^3 hapticity of the *endo*/*exo* allyl ligand. The palladium-aziridine bond is shorter than the palladium-pyridine bond (2.109(3) vs 2.158(3) Å), and the terminal allylic carbon *anti* to the aziridine form a bond with palladium (2.178(4) Å) longer than the allylic terminus *anti* to the pyridine ring (2.126(4) Å). This observation supports the hypothesis that the allylic terminus *anti* to the aziridine has a more electrophilic character. The ^{1}H NMR spectra of the CD_2Cl_2 solutions of this salt and all the other [(allyl)- or (1,3-diphenylallyl)(**10a** or **10b**)]Pd^+ salts with PF_6^-, SbF_6^- and BF^{4-} counterions were complex and showed broad absorptions, indicating the presence of several species, although the *endo*- and *exo*-(η^3-allyl) (N,N)Pd^+ species were predominant. Most importantly, in the case of the 1,3-diphenylallyl complexes, a higher ratio of rotamers (>3:1) was observed for the complex derived from the ligand **10ba'**, which afforded the

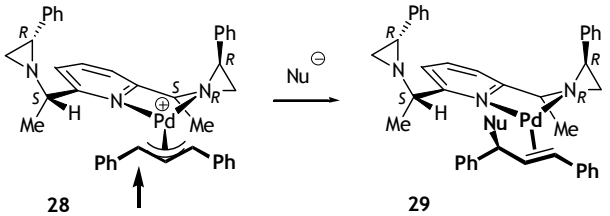
highest enantioselectivity. Moreover, the spectra were complicated by the lack of C_2-symmetry of the ligand complex, demonstrating that only one aziridine nitrogen was involved in Pd coordination. For example, for each rotamer, distinct absorptions were observed for the two benzylic protons.

In the absence of information on the reactive intermediate involved in the enantioselective step, we can only speculate on the the origin of the enantioselectivity. We take into account the available structural information of the bidentate complex **13** and the mechanistic hypothesis that has been suggested to explain the sense of asymmetric induction provided by such ligands. [8] Moreover, several studies on the binding properties of potentially terdentate ligands towards (allyl)Pd(II) cations have been reported.[17]-[19] For example, the X-ray crystal structure of a (terpyridine)(allyl)palladium complex has been determined and its dynamic behaviour in solution has been studied by ^{1}H- and ^{13}C-NMR spectroscopy.[17] It was therein shown that terpyridine binds the (η^1-allyl)Pd^+ fragment in the terdentate fashion and η^3-allyl)Pd+ as a bidentate ligand. In fact, the two species are present both in the crystal and in a CD_2Cl_2 solution in a dynamic equilibrium, which is strongly displaced towards the η^3-allyl form at low temperature. On the other hand, the 2,6-bis(diphenylphosphanylmethyl)pyridine (PNP) ligand in the complex [(PNP)(allyl)Pd][BF_4] adopts the terdentate coordination mode both in the crystal and in solution, where the complex is fluxional through η1-η3 equilibrium processes.[18][19] This is in contrast to the behaviour of (N,P,N) ligands which act as (P,N)-bidentate ligands in (η3-dimethylallyl)Pd+ complexes.[20] Similarly, the presence of the pyridine ring in a chiral (P,N,N) ligand was unnecessary for high selectivity in the AAA reaction, suggesting that the ligand acts in a (P,N)-bidentate fashion.[21]

On the basis of the precedent studies, we believe that the prevalent rotamer of the reactive (η^3-1,3-diphenylallyl)(N,N,N)Pd^+ complex is **28**, featuring the *syn*,*syn*-configuration of the allylic ligand and reduced interactions of the allylic phenyl groups and the aziridine substituent. Moreover, in solution the chiral aziridinylalkyl substituent not involved in palladium chelation should take the same spatial arrangement as observed in the crystal structure, with the methine hydrogen oriented towards the allylic ligand in order to reduce the steric interactions. Obviously, owing to the C_2-symmetry of the nitrogen ligand, identical η^3-(N,N)-complexes are formed when one or the other aziridine nitrogen is involved in Pd coordination.

If this assumption is correct, the sense of enantioselectivity is easily explained by the attack of the nucleophile on the more electrophilic allylic terminus *anti* to the aziridine

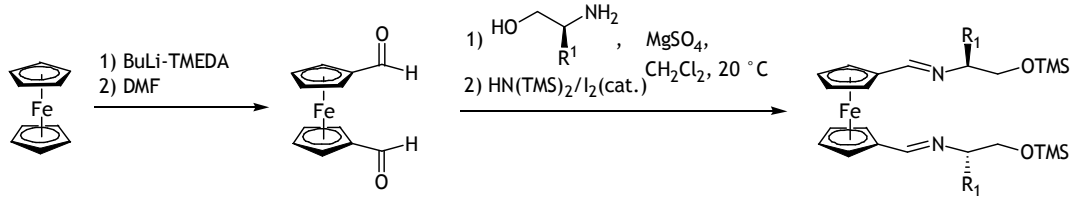
nitrogen of the intermediate **28** to give the (η^2-alkene)Pd(0) complex η^2-(N,N)-**29**. The regioselectivity of the nucleophilic attack is also favoured by the preferential clock-wise rotation of the hydrocarbon ligand occurring during the formation of the most stable (η^2-alkene)Pd complex **29**, as the steric interactions between the alkene and the nitrogen ligand are reduced concurrently.



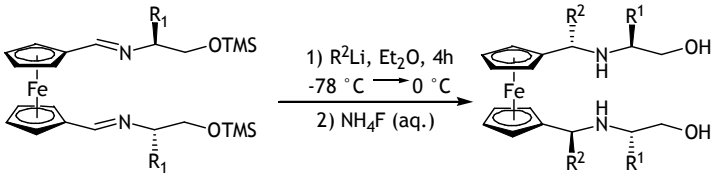
6.4. Chiral ligands featuring two aziridine rings linked by a non-chelating aromatic spacer

In the DIAZAP ligands studied before the linker between the two aziridine ring was "active" since the palladium was actually chelated by the nitrogen atom of the pyridine moiety. We wished to verify if the two aziridine rings alone could be able to chelate efficiently a metal center in a bidentate fashion, so we planned to synthesize ligands featuring two aziridines connected by different spacer: a ferrocenyl or a phenyl moiety.

The synthetic route to these new ligands was very similar to the one for Diazap ligands. We started from 1,1'-ferrocenyldicarboxaldehyde, which was easily prepared by double metallation of ferrocene in dry hexane with *n*-BuLi-TMEDA and then quenching the dilitio species with DMF. Imines were prepared in almost quantitative yields by condensation of the dialdehyde with the proper aminoalcohol (2 equivalents of valinol or phenylglycinol) and silylation of the hydroxy groups; for the latter step, we obtained the best results employing hexamethyldisilazane in dichloromethane and iodine as a catalyst.

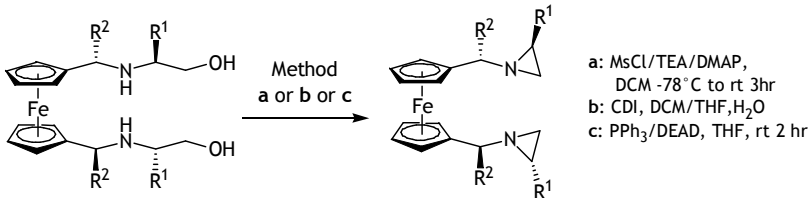


These electron rich imines were poorly reactive and only the most reactive organolithium reagents gave smoothly the corresponding diamines with satisfactory yields and diastereoselectivities.



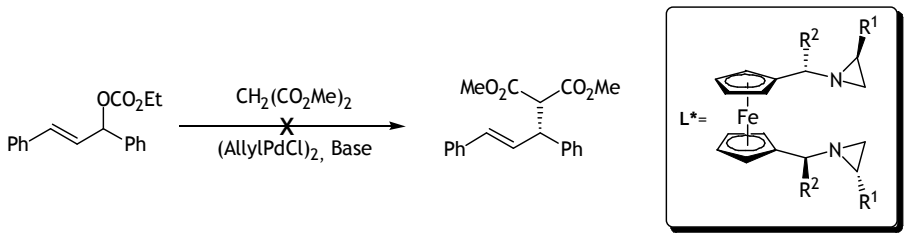
Imine	R2Li	d.r.	Resa%
R1 = *i*Pr	*n*BuLi	93:7	95
R1 = *i*Pr	*t*BuLi	99:1	96
R1 = Ph	PhLi	85:15	94
R1 = Ph	nBuLi	90:10	91

The construction of the aziridine ring from the β-aminoalcohol moiety was even more troublesome, and we were not able to find a procedure having a general applicability for every substrate. The desired aziridines were obtained only in moderate yields after considerable efforts in each case.



AminoAlcohol	Method	Yield%
R1 = *i*Pr, R2 = *n*Bu	b	68
R1 = *i*Pr, R2 = *t*But	c	50
R1 = Ph, R2 = Ph	a	47
R1=Ph, R2 = *n*Bu	a	45

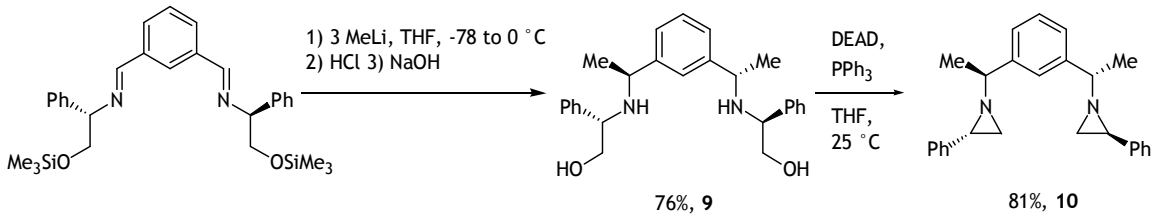
With these new ligands in hand the next step was to test them in standard AAA reactions, but with our great disappointment we found that the reaction with dimethyl malonate did not proceed with all the ligands we prepared in the standard reaction conditions (BSA, allylpalladium chloride dimer, dichloromethane).



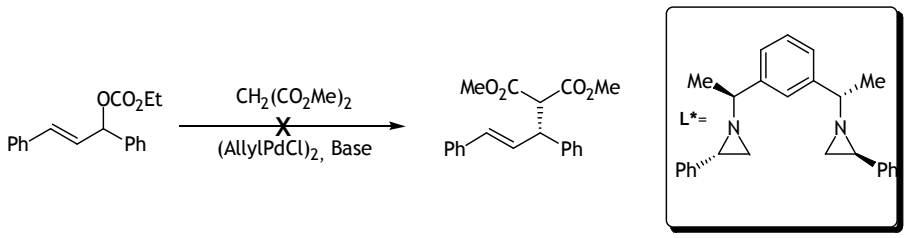
R^1	R^2	Temp.	Solvent	Base	t	Yield	e.e%
Ph	*t*-Bu	25	DCM	BSA/AcOK	24	-	-
Ph	Ph	25	DCM	BSA/AcOK	24	-	-
i-Pr	*n*-Bu	25	DCM	BSA/AcOK	24	-	-
i-Pr	*t*-Bu	25	DCM	BSA/AcOK	24	-	-

A reasonable explanation for this negative results is that these ligands can not act as bidentate ligands because of the preferred *anti*-conformation of the two cyclopentadienyl substituents, or the eventually formed bidentate complex is too labile.

Aiming to obtain a more rigid ligands, we prepared a ligand structurally similar to the previously described DIAZAP ligands, but presenting a non-chelating 1,3-disubstituted phenyl in substitution of the pyridine ring starting from isophtalaldehyde, following the usual synthetic scheme.



This new ligand proved again to be completely uneffective in the standard palladium catalysed AAA reaction of 1,3 diphenylallylcarbonate with sodium dimethylmalonate, and no considerable conversion was observed after 5 days even with 10% mol/mol catalyst loading.



These results confirm that the pyridine moiety is necessary for an efficient chelation of the metal center and, consequence to this, to achieve good conversions and enantioselectivities.

Experimental Section:

General Protocol for the Preparation of Imines: To a solution of (*S*)-valinol (6 mmol, 0.618 g) or (*S*)-phenylglycinol (6 mmol, 0.823 g) in THF (50 mL) was added anhydrous $MgSO_4$ (5 g), the aldehyde (3 mmol, 0.405 g) and the mixture was stirred overnight. The solid phase was filtered off on a pad of Celite and the organic solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and triethylamine (7 mmol, 0.708 g) and chlorotrimethylsilane (7 mmol, 0.97 mL. 0.760 g) were added at 0 °C. After 3 h the solvent was removed under vacuum. A solution of cyclohexane/diethyl ether 1:1 was added and the solid phase was filtered off on a pad of Celite. The organic solvent was evaporated under reduced pressure to leave the imine in almost quantitative yield; this was used in the following step without further purification.

Preparation of β-Aminoalcohols 9 by Addition of Organolithium Reagents to Imines 8: Organolithium reagent (9 mmol) was added to a magnetically stirred solution of the imine **8** (3 mmol) in THF (10 mL) cooled to –78 °C. After 30 minutes, the reaction mixture was slowly warmed at 0 °C, and quenched after 3 h by adding 1 N HCl (10mL). After 2 h NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 ×10 mL). The collected ethereal phases were dried over Na_2SO_4 and concentrated to leave the crude products. The diastereomeric ratio was determined by ^1H NMR analysis. Flash column chromatography (SiO_2), eluting with cyclohexane/ethyl acetate mixtures, gave the product which was directly used in the subsequent step.

Preparation of β-Aminoalcohols 9af' and 9bf' by Reduction of Imines 8a and 8b: To a solution of imine **8a** or **8b** (1 mmol) in methanol (5 mL), $NaBH_4$ (2 mmol, 0.076 g) was added in one portion. After 1 h the reaction was quenched with 1 N HCl (5 mL) and further stirred for 2 h. Then NaOH pellets were added until the solution reached pH 11, and the organic phase was extracted with diethyl ether (3 × 10 mL). The collected ethereal phases were dried over Na_2SO_4 and concentrated to leave the crude product in quantitative yield. Pure compounds were obtained by column chromatography (SiO_2) eluting with cyclohexane/ethyl acetate mixtures.

Preparation of Aziridines 10: To a solution of β-aminoalcohol **9** (2.8 mmol) in THF (20 mL) was added PPh_3 (6.2 mmol, 1.6 g). To this solution DEAD (6.2 mmol, 1.082 g) was added dropwise. After 4 h, a solution of 2 N KOH (10 mL) was added to the mixture, which was stirred for 3 h. Diethyl ether was added (30 mL) and the organic phase was separated. The aqueous phase was extracted with Et2O (3 x 20 mL), and the collected organic phase was washed with 2 N KOH (3 x 10 mL), then with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was flash-chromatographed on a SiO_2 column eluting with cyclohexane/ethyl acetate mixtures. In order to obtain analytically pure samples, further purification by chromatography or crystallization was carried out.

***N,N'*-Bis((S)-1-trimethylsilyloxy-3-methyl-butan-2-yl)-2,6-bis(imino)pyridine (8a)**: Yellowish oil; $[\alpha]_D^{25}$ = -19.7 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 0.05 (s, 18 H), 0.92 (d, *J* = 6.9 Hz, 6 H), 0.94 (d, *J* = 6.9 Hz, 6 H), 2.0 (sept, *J* = 6.9 Hz, 2 H), 3.1 (m, 2 H), 3.69 (dd, *J* = 7.8 Hz, *J* = 10.3 Hz, 2 H), 3.89 (dd , *J* = 4.3 Hz, *J* = 10.3 Hz , 2 H), 7.76 (t, *J* = 7.6 Hz, 2 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 8.36 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz): □= 0.4, 18.5, 20.0, 29.9, 64.3, 78.4, 121.9, 136.7, 154.5, 161.6; IR (neat): ν = 2958, 2872, 1648, 1585, 1569, 1457, 1251, 1107,1077, 877, 841, 746 cm^{-1}; GC-MS *m/z*: 73 (100), 171 (70), 346 (36), 103 (27), 316 (11), 449 (10, M).

***N,N'*-Bis((*S*)-2-trimethylsilyloxy-1-phenylethyl)-2,6-bis(imino)pyridine (8b)**: white solid; m.p. = 117 °C; $[\alpha]_D^{25}$ = +25.1 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 0.02 (s, 18 H), 3.89 (d, *J* = 1.7 Hz, 2 H), 3.91 (s, 2 H), 4.52 (dd, *J* = 5.6 Hz, *J* = 7.8 Hz, 2 H), 7.2-7.4 (m, 7 H). 7.5-7.6 (m, 3 H), 7.81 (t, *J* = 7.6 Hz, 1 H), 8.20 (d, *J* = 7.6 Hz, 2 H), 8.49 (s, 2 H); ^{13}C

NMR ($CDCl_3$, 50 MHz): δ = 0.4, 67.6, 76.7, 122.2, 127.4, 128.4, 136.7, 140.7, 155.4; IR (Nujol): ν= 3067, 3029, 1647, 1364, 1251, 1118, 1081, 1054, 884, 841, 757, 699 cm^{-1}.

***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-aminoethyl)pyridine (9aa')**: White solid; m.p. = 86 °C; $[\alpha]_D^{25}$ = -74.6 (c 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 0.81 (d, *J* = 6.8 Hz, 6H), 0.86 (d , *J* = 6.8 Hz, 6 H), 1.37 (d, *J* = 6.7 Hz, 6 H), 1.65 (sept, *J* = 6.8 Hz, 2 H), 2.19 (dd, *J* = 4.2 Hz, *J* = 4.8 Hz, 2 H), 2.70 (bs, 4 H), 3.38 (dd, *J* = 4.8 Hz, *J* = 10.8 Hz, 2 H), 3.61 (dd, *J* = 4.2 Hz, *J* = 10.8 Hz, 2 H), 3.89 (q, *J* = 6.7 Hz, 2 H), 7.05 (d, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 18.8, 19.6, 23.5, 29.4, 56.2, 60.0, 62.0, 119.8, 136.7, 163.7; IR (KBr): ν= 3404, 3968, 1572, 1449, 1361, 1172, 1074, 834 cm^{-1}; anal. calcd. for C19H35N3O2: C 67.62, H 10.45, N 12.45; found: C 67.37, H 10.48, N 12.41.

***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-aminopentyl)pyridine (9ab')**: Yellowish oil; $[\alpha]_D^{25}$ = -48.5 (c 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 0.77 (d, *J* = 6.8 Hz, 6 H), 0.79 (d, *J* = 6.8 Hz, 6 H), 0.82 (t, *J* = 6.6 Hz, 6 H), 1.25 (m, 8 H), 1.63 (sept, *J* = 6.8 Hz, 2 H), 1.72 (m, 4 H), 2.08 (dd, *J* = 3.8 Hz, *J* = 6.4 Hz, 2 H), 3.73 (bs, 4 H), 3.39 (dd, *J* = 3.8 Hz, *J* = 10.8 Hz, 2H), 3.61 (dd, *J* = 6.4 Hz, *J* = 10.8 Hz, 2 H), 3.62 (t, *J* = 6.9 Hz, 2 H), 6.97 (d, *J* = 7.6 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 13.9, 18.8, 19.6, 22.6, 28.7, 29.4, 37.5, 59.5, 61.3, 62.0, 120.9, 136.0, 163.2; IR (neat): ν = 3160, 2957, 2926, 2858, 1590, 1464, 1260, 1089, 801 cm^{-1}; ESI-MS *m/z*: 422.4 [M+ 1], 423.3 [M+ 2]; anal. calcd. for C25H47N3O2: C 71.21, H 11.23, N 9.97; found: C 71.08, H 11.25, N 9.93.

***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-amino-2,2-dimethylpropyl)pyridine (9ac')**: Colourless oil; $[\alpha]_D^{25}$ = -82.9 (c 1.4, $CHCl_3$); ^{1} H NMR ($CDCl_3$, 200 MHz): δ = 0.75 (d, *J* = 6.6 Hz, 6 H), 0.8 (d , *J* = 6.6 Hz, 6 H), 0.93 (s, 18 H), 1.62 (sept, *J* = 6.6 Hz, 2 H), 2.00 (dd, *J* = 3.4 Hz, *J* = 3.9 Hz, 2 H), 2.40 (bs, 4 H), 3.39 (dd, *J* = 3.4 Hz, *J* = 10.9 Hz, 2 H) 3.42 (s, 2 H), 3.62 (dd, *J* = 3.9 Hz, *J* = 10.9 Hz, 2 H), 7.00 (d, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR($CDCl_3$, 50 MHz): δ= 18.7, 19.9, 27.3, 29.6, 35.4, 59.0, 62.4, 69.9, 121.8, 131.0, 161.3; IR (Nujol): ν= 3444, 1644, 1496, 1205, 1090, 933 cm^{-1}; ESI-MS *m/z*: 422.6 [M+ 1], 423.2 [M+ 2]; anal. calcd. for C25H47N3O2: C 71.21, H 11.23, N 9.97; found: C 71.00, H 11.28, N 9.94.

***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-1-amino-4,4-dimethylpentyl)pyridine (9ad')**: Colourless oil; $[\alpha]_D^{25}$ = ~ -47.7 (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ= 0.80 (d, *J* = 6.9 Hz, 6 H), 0.82 (s, 18 H), 0.83 (d , *J* = 6.9 Hz, 6 H), 1.00 (dt, *J* = 4.4 Hz, *J* = 13.1 Hz, 2H), 1.35 (dt, *J* = 4.4 Hz, *J* = 13.1 Hz, 2 H), 1.65 (m, 6 H), 2.12 (dd, *J* = 3.9 Hz, *J* = 6.8 Hz, 2 H), 3.42 (dd, *J* = 3.9 Hz, *J* = 10.8 Hz, 2 H), 3.60 (dd, *J* = 6.8 Hz, *J* = 10.8 Hz, 2 H), 3.63 (t, *J* = 3.9 Hz, 2 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 7.55 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR($CDCl_3$, 50 MHz): δ= 18.9, 19.8, 29.3, 29.5, 30.1, 32.9, 40.7, 59.5, 62.0, 62.1, 120.7, 136.2, 163.2; IR (neat): ν= 3420, 2925, 1646, 1591, 1376, 1278, 997 cm^{-1}; anal. calcd. for C28H52N3O2: C 72.68, H 11.33, N 9.08; found: C 72.38, H 11.40, N 9.07.

***N,N'*-Bis((S)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis((*S*)-amino(phenyl)methyl)pyridine (9ae')**: Yellowish oil; $[\alpha]_D^{25}$ = + 95.7 (c 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (d, *J* = 6.9 Hz, 6 H), 0.95 (d , *J* = 6.9 Hz, 6 H), 1.92 (sept, *J* = 6.9 Hz, 2 H), 2.46 (ddd, *J* = 3.9 Hz, *J* = 6.0 Hz, *J* = 10.2 Hz, 2 H), 2.92 (bs, 2 H), 3.42 (dd, *J* = 6.6 Hz, *J* = 10.8 Hz, 2 H), 3.57 (dd, *J* = 4.2 Hz, *J* = 10.8 Hz, 2 H), 5.0 (s, 2 H), 6.92 (d, *J* = 7.8 Hz, 2 H), 7.27-7.42 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 18.2, 19.5, 30.2, 60.5, 62.1, 35.0, 120.8, 127.4, 127.9, 128.5, 136.9, 142.9, 161.2; IR (neat): ν= 3417, 3333, 3061, 3027, 2957, 2872, 1589, 1572, 1448, 1045, 839, 736, 700 cm^{-1}; ESI-MS *m/z*: 462.0 [M+ 1]; anal. calcd. for C29H39N3O2: C 75.45, H 8.52, N 9.10; found: C 75.24, H 8.65, N 9.04.

***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-aminoethyl)pyridine (9ba')**: White solid; m.p. = 95 °C; $[\alpha]_D^{25}$ = +30.7 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ= 1.40 (d, *J* = 6.6 Hz, 6 H), 3.59 (dd, *J* = 7.8 Hz, *J* = 10.8 Hz, 2 H), 3.65-3.88 (m, 6 H), 7.03 (d , *J* = 7.8 Hz, 2 H), 7.2-7.4 (m, 10 H), 7.81 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 21.4, 55.7, 61.8, 66.1, 119.3, 127.5, 127.3, 128.3, 136.8, 141.1, 162.7; IR (KBr):ν= 3383, 3065, 3032, 2973, 2930, 2846, 1577, 1458, 1327, 1233, 1096, 751, 733, 699 cm^{-1}; ESI-MS *m/z*: 406.2 [M+ 1], 428.3 [M+ Na]; anal. calcd. for C25H31N3O2: C 74.04, H 7.70, N 10.36; found: C 73.98, H 7.75, N 10. 33.

***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-aminopentyl)pyridine (9bb')**: Colourless oil; $[\alpha]_D^{25}$ = +110.3 (c 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ= 0.88 (t, *J* = 6.7 Hz, 6 H), 1.0-1.4 (m, 8 H), 1.6-1.8 (m, 4 H), 3.1 (bs, 4 H), 3.4-3.6 (m, 4 H), 3.6-3.8 (m, 4

H), 6.88 (d, *J* = 7.7 Hz, 2 H), 7.1-7.4 (m, 11 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 14.0, 22.7, 28.3, 36.4, 61.4, 62.2, 65.3, 120.2, 127.0, 127.2, 128.2, 136.0, 141.6, 162.5; IR (neat):ν = 3324, 2923, 2853, 1576, 1457, 1366, 1129, 1052, 701 cm^{-1}; anal. calcd. for C31H43N3O2: C 76.03, H 8.85, N 8.58; found: C 75.75, H 8.87, N 8.55.

***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-amino-2,2-dimethylpropyl)pyridine (9bc')**: Colourless oil; $[\alpha]_D^{25}$ = +105.0 (c 1.5, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 0.84 (s, 18 H), 3.31 (s, 2 H), 3.43 (dd, *J* = 4.8 Hz, *J* = 5.1 Hz, 2 H), 3.51 (dd, *J* = 5.1 Hz, *J* = 10.6 Hz, 2 H), 3.73 (dd, *J* = 4.8 Hz, *J* = 10.6 Hz, 2 H), 6.73 (d, *J* =7.5 Hz, 2 H), 7.00-7.10 (m, 5 H), 7.15-7.55 (m, 5 H), 7.46 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 27.1, 35.5, 63.3, 64.9, 70.0, 122.4, 128.2, 134,3, 142.0, 160.9; IR (neat):ν= 3408, 3055, 2952, 2863, 1588, 1576, 1469, 1453, 1395, 1361, 1031, 824, 757, 701 cm^{-1}; ESI-MS *m/z*: 490.4 [M+ 1], 512.3 [M+ Na]; anal. calcd. for C31H43N3O2: C 76.03, H 8.85, N 8.58; found: C 75.80, H 8.91, N 8.52.

***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis((*S*)-1-amino(phenyl)methyl)pyridine (9be')**: Colourless oil; $[\alpha]_D^{25}$ = +123.2 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 3.00 (bs, 4 H), 3.72 (m, 6 H), 4.78 (s, 2 H), 6.72 (d, *J* = 7.6 Hz, 2 H), 7.30-7.40 (m, 23 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 61.2, 64.0, 67.0, 120.4, 127.1, 127.5, 127.7, 128.3, 128.6, 128.7, 130.0, 131.5, 133.2, 136.9, 145.0, 141.7, 167.0; IR (neat):ν= 3411, 3060, 3026, 2925, 2850, 1590, 1573, 1493, 1451, 1054, 1027, 700 cm^{-1}; ESI-MS *m/z*: 530.4 [M+ 1], 531.5 [M+ 2], 552.5 [M+ Na]; anal. calcd. for C35H35N3O2: C 79.37, H 6.66, N 7.93; found: C 79.00, H 6.71, N 7.90.

***N,N'*-Bis((*S*)-1-hydroxy-3-methyl-butan-2-yl)-2,6-bis(aminomethyl)pyridine (9af')**: Colourless oil; $[\alpha]_D^{25}$ = +41.6 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 0.89 (d, *J* = 6.9 Hz, 6 H), 0.95 (d, *J* = 6.9 Hz, 6 H), 1.89 (sept, *J* = 6.9 Hz, 2 H), 2.43 (dd, *J* = 3.3 Hz, *J* = 7.5 Hz, 2 H), 3.42 (dd , *J* = 7.5, *J* = 11.1 Hz, 2 H), 3.42 (dd , *J* = 3.3, *J* = 11.1 Hz, 2 H), 3.87 (d, *J* = 14.7 Hz, 2 H), 3.97 (d, *J* = 14.7 Hz, 2 H), 7.11 (d, *J* = 7.5 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 18.6, 19.5, 29.5, 52.3, 61.4, 65.0, 120.6, 137.3, 159.5; IR (neat):ν= 3322, 2957, 2866, 1594, 1576, 1455, 1386, 1367, 1155, 1047, 787 cm^{-1}; anal. calcd. for C17H31N3O2: C 65.98, H 10.10, N 13.58; found: C 66.01, H 10.11, N 13.54.

***N,N'*-Bis((*S*)-2-hydroxy-1-phenylethyl)-2,6-bis(aminomethyl)pyridine (9bf')**: Viscous oil; $[\alpha]_D^{25}$ = +106.2 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 3.67 (m, 4 H), 3.72 (d, *J* = 14.1 Hz, 2 H), 3.80 (d, *J* = 14.1 Hz, 2 H), 3.86 (dd, *J* = 5.3 Hz, *J* = 9.6 Hz, 2 H), 4.1 (bs, 1 H), 7.0 (d , *J* = 7.6 Hz, 2 H), 7.2-7.4 (m, 10 H), 7.52 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 51.9, 64.6, 67.0, 120.6, 127.4, 127.5, 128.4, 136.8, 140.4, 158.7; IR (Nujol): ν= 3310, 3061, 3028, 2924, 2862, 1594, 1577, 1492, 1452, 1357, 1057, 1027, 759, 702 cm^{-1}; ESI-MS *m/z*: 378.3 [M + 1], 379.4 [M + 2], 400.4 [M + Na]; anal. calcd. for C23H27N3O2: C 73.18; H 7.21, N 11.13; found: C 72.83, H 7.24, N 11.10.

2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)ethyl)pyridine (10aa'): Colourless oil; $[\alpha]_D^{25}$ = -119.6 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ= 0.53 (d, *J* = 6.6 Hz, 6 H), 0.75 (d, *J* = 6.6 Hz, 6 H), 1.10 (sept, *J* = 6.6 Hz, 2 H), 1.22 (m, 2 H), 1.33 (d, *J* = 6.3 Hz, 2 H), 1.38 (d, *J* = 6.6 Hz, 6 H), 1.63 (d, *J* = 3.3 Hz, 2 H), 2.53 (q, *J* = 6.6 Hz, 2 H), 7.37 (d , *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.5, 20.4, 21.2, 31.4, 32.6, 45.8, 71.6, 119.6, 136.7, 162.7; IR (neat): ν = 3041, 2962, 1591, 1576, 1460, 1327, 1176, 822 cm^{-1}; GC-MS *m/z*: 56 (100), 55 (87), 84 (63), 132 (35), 218 (18), 162 (9); anal. calcd. for C19H31N3: C 75.70, H 10.36, N 13.94; found: C 75.78, H 10.41, N 13.88.

2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)pentyl)pyridine (10ab'): Colourless oil; $[\alpha]_D^{25}$= -140.7 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.47 (d, *J* = 6.5 Hz, 6 H), 0.74 (d, *J* = 6.5 Hz, 6 H), 0.78 (t, *J* = 7.0 Hz, 6 H), 0.86 (m, 2 H), 1.04 (m, 2 H), 1.21 (m, 8 H), 1.40 (d, *J* = 6.3 Hz, 2 H), 1.67 (d, *J* = 3.6 Hz, 2 H), 1.88 (q, *J* = 7.6 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 7.31 (d , *J* = 7.6 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.1, 19.9, 20.6, 22.0, 28.6, 31.9, 34.2, 35.9, 45.0, 77.3, 120.8, 136.7, 162.1; IR (neat): ν= 3040, 2957, 2871, 1591, 1576, 1457, 1364, 1029 cm^{-1}; GC-MS *m/z*: 84 (100), 302 (75), 259 (53), 174 (35), 55 (30), 385 (1, M); anal. calcd. for C25H43N3: C 77.86, H 11.24, N 10.90; found: C 77.58, H 11.26, N 10.85.

2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)-2,2-dimethylpropyl)pyridine (10ac'): White solid; m.p. = 84 °C; $[\alpha]_D^{25}$= -18.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 0.53 (d, *J* = 6.6 Hz, 6 H), 0.72 (d, *J* = 6.6 Hz, 6 H), 0.98 (m, 2 H), 0.99 (s, 18 H), 1.18 (sept, *J* = 6.6 Hz, 2 H) 1.49 (d , *J* = 6.3 Hz, 2 H), 1.76 (d, *J* = 3.9 Hz, 2 H), 2.73 (s, 2 H), 7.33 (d , *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 19.6, 20.8, 27.8, 30.8, 36.3,

36.7, 42.8, 85.5, 122.4, 134.4, 160.2; IR (KBr): $\tilde{\nu}$= 3064, 2873, 1588, 1571, 1497, 1449, 1286, 1031, 872 cm^{-1}; anal. calcd. for C25H43N3: C 77.86, H 11.24, N 10.90; found: C 77.91, H 11.28, N 10.86.

2,6-Bis((*S*)-1-((*S*)-2-isopropylaziridin-1-yl)-4,4-dimethylpentyl)pyridine (10ad'): Colourless oil; $[\alpha]_D^{25}$ = -149.5 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.50 (d, *J* = 6.6 Hz, 6 H), 0.79 (d, *J* = 6.6 Hz, 6 H), 0.83 (s, 18 H), 1.10 (sept, *J* = 6.6 Hz, 2 H), 1.17-1.37 (m, 6 H), 1.43 (d, *J* = 6.5 Hz, 2 H), 1.70 (d, *J* = 3.5 Hz, 2 H), 1.91 (dt, *J* = 7.1 Hz, *J* =9.8 Hz, 4 H), 2.40 (t, *J* = 7.1 Hz, 2 H), 7.36 (d , *J* = 8.0 Hz, 2 H), 7.68 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 19.7, 20.4, 29.2, 30.1, 31.1, 31.7, 34.0, 40.0, 44.7, 77.5, 120.6, 136.6, 161.9; IR (neat): $\tilde{\nu}$= 3060, 2879, 1591, 1568, 1490, 1450, 1281, 1038, 878 cm^{-1}; GC-MS *m/z*: 57 (100), 84 (92), 56 (71), 287 (28), 258 (22), 132 (16), 202 (12); anal. calcd. for C29H51N3: C 78.85, H 11.64, N 9.51; found: C 78.75, H 11.68, N 9.47.

2,6-Bis((*S*)-((*S*)-2-isopropylaziridin-1-yl)(phenyl)methyl)pyridine (10ae'): Yellowish oil; $[\alpha]_D^{25}$ = -158.3 (c 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.47 (d, *J* = 6.6 Hz, 6 H), 0.82 (d, *J* = 6.6 Hz, 6 H), 1.23 (m, 2 H), 1.44 (d , *J* = 7.2 Hz, 2 H), 1.54 (dd, *J* = 3.6 Hz, *J* = 7.2 Hz, 2 H), 3.78 (s, 2 H), 7.25-7.39 (m, 8 H), 7.54-7.62 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 19.5, 20.2, 31.4, 46.4, 79.8, 120.9, 126.9, 127.4, 128.1, 137.9, 142.4, 151.0; IR (neat): $\tilde{\nu}$= 3071, 2933, 2862, 1589, 1573, 1455, 1306, 1258, 1029, 699 cm^{-1}; ESI-MS *m/z*: 426.1 [M + 1], 427.2 [M + 2]; anal. calcd. for C29H35N3: C 81.84, H 8.29, N 9.87; found: C 81.78, H 8.32, N 9.84.

2,6-Bis(((*S*)-2-isopropylaziridin-1-yl)methyl)pyridine (10af'): Colourless oil; $[\alpha]_D^{25}$ = -97.5 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ= 0.89 (d, *J* = 6.6 Hz, 6 H), 0.91 (d, *J* = 6.6 Hz, 6 H), 1.30 (m, 2 H), 1.37 (dd, *J* = 3.3 Hz, *J* = 6.3 Hz, 2 H), 1.41 (d, *J* = 6.3 Hz, 2 H), 1.69 (d, *J* = 3.3 Hz, 2 H), 3.48 (d, *J* = 14.0 Hz, 2H), 3.59 (d, *J* = 14.0 Hz, 2 H), 7.44 (d, *J* = 7.7 Hz, 2 H), 7.69 (t, *J* = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 19.6, 20.6, 31.6, 33.2, 46.7, 66.6, 120.6, 136.9, 158.6; IR (neat): $\tilde{\nu}$= 3044, 2958, 2872, 1592, 1578, 1458, 1363, 1340, 1287, 1035, 896, 829, 783 cm^{-1}; anal. calcd. for C17H27N3: C 74.68, H 9.95, N 15.37; found: C 74.22, H 9.99, N 15.33.

2,6-Bis((*S*)-1-((*S*)-2-phenylaziridin-1-yl)ethyl)pyridine (10ba'): White solid; m.p. = 79 °C; $[\alpha]_D^{25}$ = +176.6 (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ= 1.52 (d, *J* = 6.6 Hz, 6 H), 1.89 (d, *J* = 6.6 Hz, 2 H), 2.06 (d, *J* = 3.3 Hz, 2 H), 2.50 (dd , *J* = 3.3 Hz, *J* = 6.6 Hz, 2 H), 2.84 (q, *J* = 6.6 Hz, 2 H), 7.17-7.29 (m, 10H), 7.36 (d, *J* = 8.1 Hz, 2 H), 7.46 (t , *J* = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 21.6, 37.3, 40.8, 71.7, 118.8, 126.1, 126.6, 128.1, 137.3, 140.0, 162.5; IR (KBr): ν= 3032, 2972, 1576, 1580, 1459, 1326, 1207, 1095, 815, 698 cm^{-1}; ESI-MS *m/z*: 370.4 [M+ 1], 371.4 [M + 2], 392.4 [M+ Na]; anal. calcd. for C25H27N25: C 81.26, H 7.37, N 11.37; found: C 81.01, H 7.39, N 11.34.

2,6-Bis((*S*)-1-((*S*)-2-phenylaziridin-1-yl)pentyl)pyridine (10bb'): Yellowish oil; d.r. 91:9; $[\alpha]_D^{25}$ = +124.5 (c 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δmajor diastereomer) = 0.86 (t, *J* = 6.6 Hz, 6 H), 1.2-1.4 (m, 8 H), 1.92 (d, *J* = 6.2 Hz, 2 H), 1.94 (m, 2 H), 2.09 (d, *J* = 3.2 Hz, 2 H), 2.45 (dd, *J* = 3.2 Hz, *J* = 6.2 Hz, 2 H), 2.77 (dd, *J* = 6.2 Hz, *J* = 7.0 Hz, 2 H), 7.07-7.27 (m, 10 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 7.47 (t, *J* = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 14.0, 23.0, 26.9, 28.1, 36.1, 38.4, 39.4, 119.9, 126.3, 126.6, 128.1, 137.0, 146.2, 161.7; IR (neat): ν= 3031, 2978, 1574, 1588, 1454, 1329, 1198, 1092, 818, 701 cm^{-1}; anal. calcd. for C31H39N3: C 82.07, H 8.66, N 9.26; found: C 82.23, H 8.80, N 9.22.

2,6-Bis((*S*)-2,2-dimethyl-1-((*S*)-2-phenylaziridin-1-yl)propyl)pyridine (10bc'): Colourless oil; $[\alpha]_D^{25}$ = +132.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.06 (s, 18 H), 1.97 (d, *J* = 6.4 Hz, 2 H), 2.07 (dd, *J* = 3.2 Hz, *J* = 6.4 Hz, 2 H), 2.14 (d, *J* = 3.2 Hz, 2 H), 2.67 (s, 2 H), 7.07-7.40 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ= 27.5, 36.5, 37.6, 42.9, 85.4, 121.6, 126.1, 126.3, 128.0, 141.0, 151.0, 159.4; IR (neat): ν= 3033, 2974, 1572, 1584, 1456, 1323, 1187, 1097, 813, 705 cm^{-1}; anal. calcd. for C31H39N3: C 82.07, H 8.66, N 9.26; found: C 82.12, H 8.70, N 9.25.

2,6-Bis((*S*)-phenyl((*S*)-2-phenylaziridin-1-yl)methyl)pyridine (10be'): Colourless oil; d.r. 92:8; $[\alpha]_D^{25}$ = +104.5 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δmajor diastereomer)= 2.00 (d, *J* = 6.4 Hz, 2 H), 2.13 (d, *J* = 3.5 Hz, 2 H), 2.79 (dd, *J* = 3.5 Hz, *J* = 6.4 Hz, 2 H), 4.06 (s, 2 H), 7.17-7.74 (m, 23 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.0, 41.2, 79.5, 120.0, 126.3, 126.6, 126.8, 127.1, 127.7, 128.1, 128.2, 137.3, 140.0, 142.2, 161.3; IR (neat): ν= 3036, 2974, 1575, 1586, 1453, 1324, 1203, 1096, 829, 679 cm^{-1}; ESI-MS *m/z*: 494.5 [M + 1], 495.5 [M + 2]; anal. calcd. for C35H31N3: C 85.16, H 6.33, N 8.51; found: C 84.92, H 6.35, N 8.48.

2,6-Bis(((*S*)-2-phenylaziridin-1-yl)methyl)pyridine (10bf'): Colourless oil; $[\alpha]_D^{25}$ = +124.3 (c 1.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ= 1.92 (d, *J* = 6.6 Hz, 2 H), 2.03 (d , *J* = 3.2 Hz, 2 H), 7.03 (dd, *J* = 3.2 Hz, *J* = 6.6 Hz 2 H), 3.65 (d, *J* = 15.0 Hz 2 H), 3.91 (d, *J* = 15.0 Hz, 2 H) 7.20-7.74 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 38.1, 41.6, 66.3, 120.1, 126.1, 126.9, 128.3, 128.4, 128.6, 131.9, 132.0, 132.2, 137.3, 140.1, 158.3; IR (neat):ν = 3031, 2978, 1570, 1586, 1461, 1321, 1204, 1095, 819, 694 cm^{-1}; anal. calcd. for C23H23N3: C 80.90, H 6.79, N 12.31; found: C 81.15, H 6.83, N 12.30.

Preparation of allylic palladium complexes. Typical procedure: [10ae'(η^3-allyl)Pd][PF_6]. Allyl palladium chloride dimer (73 mg, 0.1 mmol) was added to a solution of ligand **10ae'** (80 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) in one portion. After one hour a solution of NH_4PF_6 (39 mg, 0.24 mmol) in THF (1mL) was added. The solution was stirred overnight, then filtered through a HPLC filter (0.45 μm) and the solvent was removed under reduced pressure to give a white solid: 0.130 g, 91%. White crystals, suitable for X-ray diffraction analysis were obtained from a double-layer of CH_2Cl_2 and pentane: white crystals; m.p. 124-126 °C (dec.); $[¤]_D^{20}$ +21.1 (c 1.2, $CHCl_3$); IR (KBr) 3052**,** 3030, 2882, 1605, 1567, 1496, 1452, 1265, 1014, 840, 732, 701, 553 cm^{-1}**.**

The 1H NMR spectra of all the allyl and 1,3-diphenylallyl cationic Pd complexes synthesized showed the presence of different species, but the *exo* and *endo* rotamers were prevalent with variable ratios. Specifically, the spectrum of the complex **10ae'**(1,3-diphenylallyl)PdPF6 (600 MHz, CDCl3) showed a 55:45 ratio of two rotamers, with the following absorptions of the allylic protons: major rotamer, δ = 5.98 (t, *J* =11.4 Hz, 1 H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H) ppm; minor rotamer, δ= 6.13 (t, *J* = 11.4 Hz, 1 H), 5.0 (d, *J* = 11.4 Hz, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H) ppm. On the other hand, the 1H NMR spectrum (300 MHz, CDCl3) of **10ba'**(1,3-diphenylallyl)PdPF6 showed the presence of a prevalent species (ca 75%) with the *syn,syn* geometry of the allylic ligand, whose protons gave absorptions at δ= 6.16 (t, *J* = 11.4 Hz, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H) and 3.80 (d, *J* = 11.4 Hz, 1 H).

[(10ae')(allyl)Pd][PF6]. X-Ray details: Bruker APEX II CCD diffractometer (Mo-Kα radiation λ = 0.71073 Å). Results: $C_{32}H_{40}F_6N_3PPd$, M_r = 718.04, monoclinic $P2_1$, *a* = 11.0990(13), *b* = 13.3802(16), *c* = 11.9282(14)Å, ¤ = 112.045(2), V = 1641.9(3)$Å^3$, Z = 2, ρ_x 1.452 Mgm^{-3}, μ 0.674 mm^{-1}, *F*(000) = 736, *T* = 296(2) K, θ_{max} = 28.51, 13905 reflections collected, 6099

I>2σ(I). Final R1 = 0.0347, wR2 = 0.0860, GOF = 0.997, absolute structure parameter = ~0.04(2).CCD 297723. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 297723. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

Palladium-Catalyzed Allylic Alkylation: To a solution of DIAZAP **10ba'** (0.03 mmol, 10 mg) in CH_2Cl_2 (2 mL) was added $(allylPdCl)_2$ (0.014 mmol, 5 mg) and the solution was degassed and stirred for 1h. 1,3-diphenyl-2-propenyl ethyl carbonate (**14b**) (0.27 mmol, 76 mg) was then added followed by dimethyl malonate (0.67 mmol, 90 mg), BSA (0.81 mmol, 0.165 g) and KOAc (0.02 mmol, 2 mg) after 10 min. The reaction was monitored by TLC analysis and, when complete, quenched with 1 N HCl solution (1 mL) and the organic phase was extracted with diethyl ether (3 ×10 mL). The organic layer was dried over Na_2SO_4 and the solvents were evaporated to dryness. The crude product was purified by chromatography on a silica gel column (hexane/AcOEt, 75:5) affording methyl (*R*)-(*E*)-3,5-diphenyl-2-methoxycarbonyl-4-pentenoate (**15**): 73 mg, 84%. An e.e. of 99% was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane1:9, 1.0 mL/min; 250 nm). retention times: 10.7 min (major enantiomer), 14.9 min (minor enantiomer).

17a: 88%, e.e. 97%; $[\alpha]_D^{25}$ -38.7 (c 2.0, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 3:97; 1.0 mL/min, 250 nm); retention times: 16.6 min (major enantiomer), 17.1 min (minor enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[13e]

17b: 89%, e.e. 99%; $[\alpha]_D^{25}$= -48.4 (c 1.5, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak AD; 2-propanol/hexane 1:99, 0.8 mL/min, 250 nm); retention times: 8.3 min (minor enantiomer), 10.9 min (major enantiomer). The absolute configuration was assumed by analogy with compound **17a**.

19: 40%, e.e. 6%; $[\alpha]_D^{25}$ = +5.0 (c 1.1, $CHCl_3$). The e.e. was determined by chiral GC: Megadex Chiral column (25 m, flow rate: 15mL/min, 50 °C (2 min), then 3 °C/min up to 190 °C, FID detection): retention times: 27.2 min (minor enantiomer), 27.3 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[14]

21: 85%, e.e. 28%, $[\alpha]_D^{25}$ = +6.5 (c 1.2, CHCl3). The e.e. was determined by chiral GC (Megadex Chiral column (25 m, flow rate: 15mL/min, isotherm 65 °C, FID detection);

retention times: 49.5 min (minor enantiomer), 51.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[15]

23-24: The ratio was determined by GC-MS analysis. The e.e.s of **23** and **24** were determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 1:99, 0.5 mL/min, 250 nm); retention times of **24**: 14.2 min (major enantiomer), 15.1 min (minor enantiomer); retention times of **23**: 17.9 (minor enantiomer), 18.8 (major enantiomer).

27: 83%, e.e. 27%; $[\alpha]_D^{25}$ = ~-23.5 (c 1.6, $CHCl_3$). The e.e. was determined by chiral HPLC (Chiralpak OD, 2-propanol/hexane 5:95, 0.4 mL/min, 250 nm); retention times: 13.7 min (minor enantiomer), 15.6 min (major enantiomer). The absolute configuration of the product was determined by comparison of its optical rotation with that of the known compound.[16b]

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