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# Preparation of pyridinyl aryl methanol derivatives by enantioselective hydrogenation of ketones using chiral Ru(diphosphine)(diamine) complexes. Attribution of their absolute configuration by $^1$H NMR spectroscopy using Mosher's reagent

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ABSTRACT

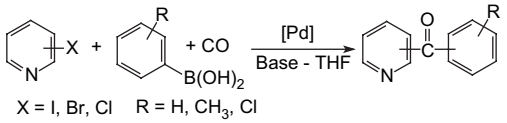
Ruthenium–diamine–diphosphine complexes provide highly efficient catalysts for enantioselective hydrogenation of a series of pyridinyl aryl ketones. The hydrogenation proceeds under mild conditions providing chiral pyridinyl aryl methanol derivatives with consistently high yields and moderate to excellent enantioselectivities (up to 99% ee) according to the structure of the chiral diphosphine. NMR studies, based on Mosher's ester derivatisation, allowed to determine the configuration of the major alcohol obtained during asymmetric hydrogenation.



## 1. Introduction

The conversion of prochiral ketones into enantiomerically pure secondary alcohols is an area of organic synthesis that continues to attract widespread interest due to the importance of this class of alcohols, particularly heterocyclic derivatives, in the field of pharmaceutical, agrochemical and otherwise biologically relevant compounds.[1] Among the various catalytic strategies available for enantioselective reduction of ketones, i.e., hydroboration,[2] hydrosilylation,[3] transfer hydrogenation,[4] alcohol dehydrogenase[5] and hydrogenation,[6] the last one appears the most attractive from atom economy and clean and friendly processes considerations. In this area, a major breakthrough was the discovery by Noyori of the extremely highly efficient ruthenium catalysts of general formula *trans* RuCl(H)(diphosphine)(diamine), which are relevant both in terms of activity and in terms of enantioselectivity.[7] Recently, such catalysts have also been applied successfully in the enantioselective hydrogenation of diaryl ketones and, interestingly, heteroaromatic ketones.[8,9]

In this context, we have recently reported on the palladium catalysed three components cross coupling of pyridine halides, carbon monoxide and boronic acids (carbonylative Suzuki coupling) as a straightforward access to a diversity of pyridinyl aryl ketones (Scheme 1).[10]




**Scheme 1.** Synthesis of pyridinyl aryl ketones via carbonylative Suzuki coupling.

This class of ketones furnishes interesting substrates for asymmetric hydrogenation into pyridinyl aryl methanol derivatives. Here, we report on the enantioselective hydrogenation of a series of pyridinyl aryl ketones performed in the presence of Noyori type catalysts and on the determination of the configuration of the prevalent hydroxy products.

## 2. Results and discussion

Various chiral diamines and atropisomeric diphosphines have been combined with success on ruthenium and used in asymmetric hydrogenation of simple ketones with very high substrate/catalyst (S/C) ratios.[6a] In particular, the diamine DAIPEN and the diphosphines of the BINAP family provide excellent chiral auxiliaries for

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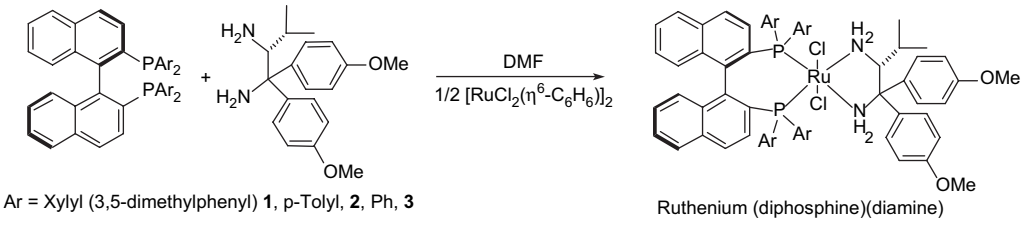



**Scheme 2.** Synthesis of ruthenium precatalysts.

highly selective ruthenium hydrogenation catalysts applicable to a large array of ketonic substrates.[8] The hydrogenation of some pyridinyl aryl ketones has already been described.[9] Basically, only one catalytic system based on Ru–XylBINAP–DAIPEN has been reported. For our study, we have chosen to combine (*R*)-DAIPEN and three BINAP's, i.e., (*R*)-XylBINAP, (*R*)-*p*-TolBINAP and (*R*)-BINAP in order to investigate the influence of the substituents on the phenyl residues on the phosphorous atoms of the chiral auxiliary. Thus, we prepared the corresponding ruthenium precatalysts **1**–**3** following reported procedures (Scheme 2).[4b] The first attempts of hydrogenation were carried out on phenyl pyridinyl methanone **4a** as a model substrate while varying the substrate/catalyst (S/C) ratios and the chiral diphosphine (Scheme 3).

The results are reported in Table 1. The first experiment carried out with precatalyst **1** at a low S/C ratio in the presence of KOH showed the efficiency of the catalytic system as the hydroxy product was obtained quantitatively with 70% ee (entry 1). In the absence of molecular hydrogen, the conversion reached only 2% after 40 h showing that the transfer hydrogenation is a minor process in the catalytic conditions (entry 2).[6a] At a higher S/C ratio (S/C=1000), a conversion of 50% and an enantioselectivity of 70% ee were obtained within 0.5 h with the same catalyst (entry 3). When increasing further the S/C ratio the process became sluggish (entry 4). Lowering the reaction temperature to 0 °C led to the improvement of the enantioselectivity to 80% ee but the reaction rate decreased significantly (entry 5). Precatalyst **2** provided a less selective catalyst than **1** (entry 6 vs 3). Performing the hydrogenation under atmospheric pressure of molecular hydrogen induced a markedly decrease of the reaction rate but has no influence on the enantioselectivity (compare entries 6 and 7). Finally, among the three diphosphine used, XylBINAP appeared the most appropriate for the hydrogenation of **4a** (70–80% ee) (entries 1, 3, 5, 6–8).

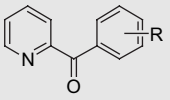
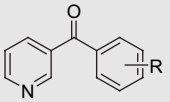
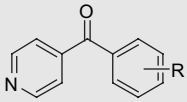
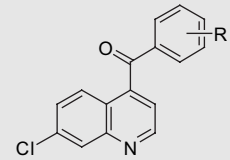
We then examined the hydrogenation of a series of pyridinyl aryl methanones prepared via carbonylative Suzuki coupling[10] in the presence of the three precatalysts **1**–**3**. The results are summarised in Table 2. Despite structural similarities, the substrates proved to behave differently under the hydrogenation conditions and no general stereoelectronic trend could be deduced from these results. Nevertheless, we observed that BINAP based catalysts are affording commonly lower selectivities (8–42% ee) than those bearing XylBINAP or *p*-TolBINAP. Still, one substrate, **5b**, was hydrogenated with 93% ee in the presence of BINAP (entry 6). In addition, we can roughly estimate that aryl ketones bearing pyridin-3-yl moieties (**5a**–**5d**, entries 5–8) were hydrogenated with higher selectivities than their homologues with pyridin-2-yl (**4a**–**4d**, entries 1–4) and pyridin-4-yl (**6a**, entry 9) or chloroquinoline (**7a**–**7c**, entries 10–12) residues.

**Table 1**
Asymmetric hydrogenation of **4a**[a]

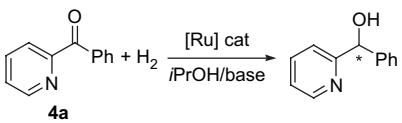
| Entry | Time (h) | [Ru][b] | S/C | Conv[c] (%) | ee[d] (%) | TOF ($h^{-1}$) |
|---|---|---|---|---|---|---|
| 1 | 15 | **1** | 100/3 | 100 | 70 | — |
| 2 | 40 | **1** | 100/3 | 2[e] | nd | — |
| 3 | 0.5 | **1** | 1000/1 | 50 | 70 | 1000 |
| 4 | 0.5 | **1** | 10,000/1 | 2 | nd | 400 |
| 5 | 2 | **1** | 1000/1 | 10[f] | 80 | 50 |
| 6 | 1 | **2** | 1000/1 | 99 | 33 | 990 |
| 7 | 4 | **2** | 1000/1 | 11[g] | 33 | 27.5 |
| 8 | 1 | **3** | 1000/1 | 81 | 14 | 810 |

[a] General conditions: **4a**=0.1 mmol, KOH/[Ru]=5/1, *i*-PrOH: 3 mL, 30 °C, $P_{H2}$=20 bar.
[b] Ruthenium precatalysts.
[c] Determined by $^1$H NMR.
[d] Determined by HPLC on a Chiralpack AD column.
[e] Reaction carried out without $H_2$ under 20 bar of $N_2$.
[f] Reaction carried out at 0 °C.
[g] Reaction performed under 1 bar of $H_2$.

**Table 2**
Hydrogenation of pyridinyl aryl methanones[a]

| Entry | Ketone | R | Cata. product | **3** ee[b] (%) | **2** ee[b] (%) | **1** ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  | **4a** H | **8a** | 14 | 33 | 70 |
| 2 | | **4b** *o*-$CH_3$ | **8b** | 20 | 34 | 99 |
| 3 | | **4c** *p*-$CH_3$ | **8c** | 8 | 40 | 60 |
| 4 | | **4d** *m*-Cl | **8d** | 15 | 9 | 50 |
| 5 |  | **5a** H | **9a** | 41 | 50 | 69 |
| 6 | | **5b** *o*-$CH_3$ | **9b** | 93 | 79 | −68[c] |
| 7 | | **5c** *p*-$CH_3$ | **9c** | 42 | 50 | 78 |
| 8 | | **5d** *m*-Cl | **9d** | 19 | 24 | 55 |
| 9 |  | **6a** H | **10a** | 17 | 32 | 54 |
| 10 |  | **7a** H | **11a** | 31 | 3 | 90 |
| 11 | | **7b** *o*-$CH_3$ | **11b** | 20 | 25 | −13[c] |
| 12 | | **7c** *p*-$CH_3$ | **11c** | 12 | −25[c] | −80[c] |

[a] General conditions: ketone=1 mmol, ketone/KOH/[Ru]=1000/5/1, *i*-PrOH: 3 mL, 30 °C, $P_{H2}$=20 bar. All conversions were >99% as determined by $^1$H NMR. The pure alcohols were isolated after silica gel chromatography in good yields (80–95%).
[b] Enantiomeric excess (ee) determined by HPLC on Chiralpack AD column. Determination of the configuration, see text.
[c] A negative ee indicate that the opposite enantiomer is formed preferentially.




**Scheme 3.** Hydrogenation of phenyl pyridinyl methanone **4a**.

Compared to the catalyst modified by BINAP (obtained from **3**), the more sterically demanding complex **2** $RuCl_2$[(*R*)-DAIPEN][(*R*)-*p*-TolBINAP] led generally to a catalyst exhibiting slightly better enantioselectivities (Δee=+5 to +32%) with the exception of hydrogenation of **4d** (entry 4), **5b** (entry 6), **7a** (entry 10) for which the enantioselectivity dropped significantly (Δee=− 6, −14 and −29%,

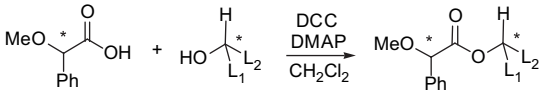
respectively) and **7c** (entry 12) as the opposite enantiomer was obtained with a moderate selectivity of 25% ee.

Finally, the Ru[(*R*)-DAIPEN][(*R*)-XylBINAP] based catalyst was found generally as the more convenient for the hydrogenation of pyridyl aryl methanones, with ee ranging from 50 to 99%. As in the case of *p*-TolBINAP (precatalyst **2**), the use of XylBINAP (precatalyst **1**) as ligand induced sometimes the formation of the opposite prevalent enantiomer than the one obtained in the presence of BINAP (precatalyst **3**) (entries 6, 11 and 12). Furthermore, it is of interest to note that the hydrogenation of **4a**, **5a** and **6a** proceeded with quite high enantioselectivities (70, 69 and 54% ee, respectively, entries 1, 5 and 9) while considering the low steric differentiation exhibited by the unsubstituted phenyl and pyridine residues of the substrates.

As mentioned above, no clear trend could be deduced for the impact of electronic and steric properties of the substrate phenyl substituents on the course of the hydrogenation reaction. Indeed, the presence of a methyl group at the ortho position of the aryl moiety improved the enantioselectivity into the hydrogenated product either slightly (entry 2 vs 1, precatalyst **3**, **4b**/**4a**, Δee=+6%) or significantly (entry 2 vs 1, precatalyst **1**, **4b**/**4a**, Δee=+29%; entry 6 vs 5, precatalyst **3**, **5b**/**5a**, Δee=+52% and precatalyst **2**, Δee=+29%). On the contrary, for the quinoline substrates, a methyl residue at the ortho position of the aryl moiety led to a significant decrease of the enantioselectivity (entry 11 vs 10, precatalyst **3**, **7b**/**7a**, Δee=−9% and catalyst **1**, Δee=−77% opposite enantiomer).

Among the alcohols obtained during our hydrogenation investigations, only four have been described in the literature.[10] Thus, we assigned the absolute configuration of the major enantiomer of the other hydrogenation products by an NMR study after derivatisation. The configuration attribution was based on the work of Riguera on aromatic shielding effects in ground state conformation of diastereomeric aryl-methoxy-acetic acid esters.[11] As such, the $^1$H NMR chemical shift comparison of the diastereomeric esters obtained from reaction of methoxy-phenyl-acetic acid (MPA) of known configuration with the different alcohols was anticipated to allow to determine the configuration of the prevalent hydrogenation product.[12]

The esterification reaction was carried out in dichloromethane with 4-dimethyl-aminopyridine (DMAP) as catalyst and dicyclohexyl-carbodiimide (DCC) (Scheme 4).[13]




**Scheme 4.** Synthesis of methoxy-phenyl-acetic acid esters.

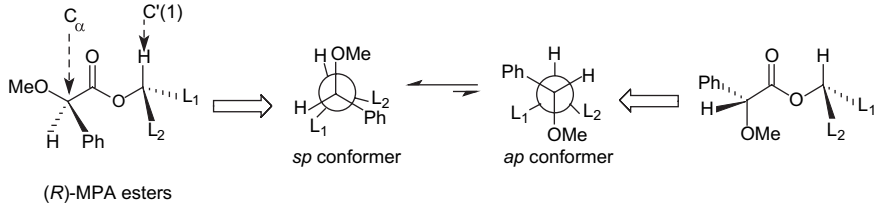
The esters obtained from the reaction of enantiopure MPA (*R* or S) with secondary alcohols can exhibit several conformations in equilibrium in solution (Scheme 5). It has been shown by Riguera that, in the case of MPA esters, only two main conformers, i.e., synperiplanar (*sp*) and antiperiplanar (*ap*) can be considered.[14] The *sp* conformer in which the **C**α-OMe, the **CO** and the **C**(1′)H bonds are co-planar is the more stable.

Thus, the substituents $L_1$ and $L_2$ of the esters prepared from (*R*)-MPA are located in such a way that the $^1$H NMR signal of the $L_2$ residue is shielded by the phenyl ring of MPA in the *sp* conformer and unaffected in the *ap* conformer while in the (*S*)-MPA ester (not shown on Scheme 5), $L_2$ is shielded in the *ap* conformer and unaffected in the *sp* conformer.

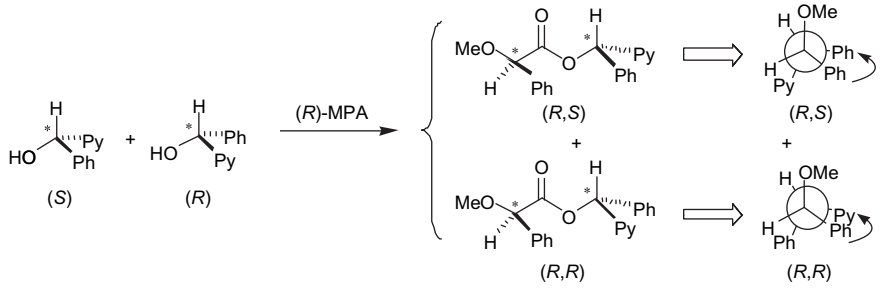
As the *sp* conformer is dominant in esters in solution, $L_2$ will resonate in the (*R*)-MPA ester at higher field than in the (*S*)-MPA ester. On the other side, $L_1$ substituent will resonate at a higher field in the (*S*)-MPA esters than in the (*R*)-MPA esters. Thus, by analysing the $^1$H NMR spectra of MPA esters, we should be able to deduce the relative location of substituent $L_1$ and $L_2$ and consequently the configuration of the corresponding alcohol.

To illustrate the application of this method, we detail below the results obtained with pyridinyl phenyl methanol **8a** (Scheme 6).

Figure 1 shows the $^1$H NMR spectra of both diastereomeric esters and that of a mixture of both. 2D NMR experiments have allowed to assign the signals of the four protons of the pyridinyl group as indicated on the spectra. We could notice that the chemical shifts of the pyridinyl protons of the two diastereomers ($H^3$–$H^6$ and $H^{3'}$–$H^{6'}$) were well resolved and appeared at quite different chemical shifts. In addition, the spectrum of one isomer is




**Scheme 5.** NMR-significant conformers of (*R*)-MPA esters.




**Scheme 6.** Esters obtained from (*R*)-MPA and a racemic mixture of pyridinyl phenyl methanol **8a**.

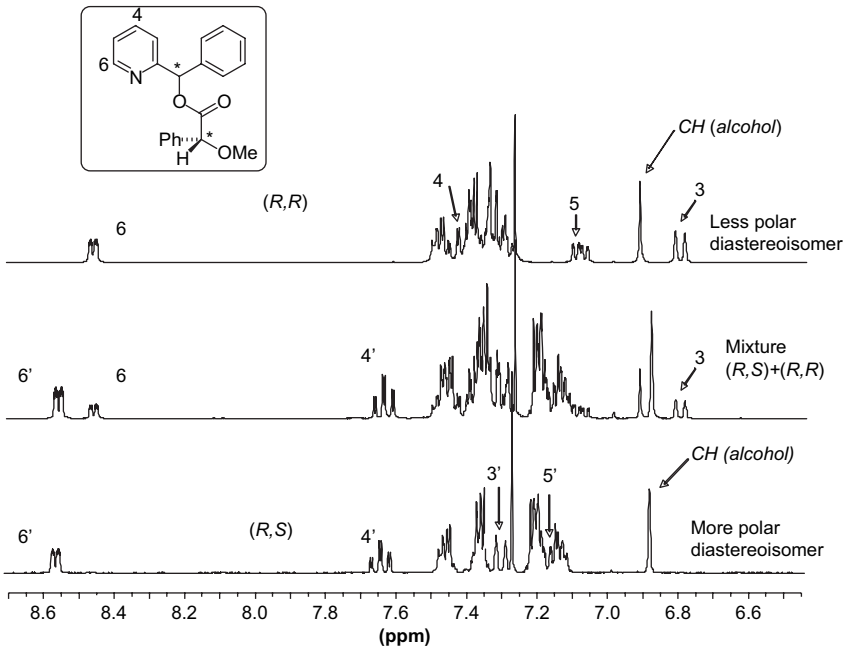



**Figure 1.** Partial $^1$H NMR spectra of (*R*)- and (*S*)-**8a** esters of (*R*)-MPA (a) less polar diastereomer (b) mixture of diastereomers (c) more polar diastereomer.

presenting proton signals of the pyridine residue at higher field than the other. In this isomer, the pyridine moiety is thus influenced by the close proximity with the phenyl residue of MPA.

From the structure of the more stable *sp* conformer, we could attribute the (*R*,*R*) configuration to the product presenting the more shielded signals of the pyridinyl protons in the $^1$H NMR spectrum. On the other side, the $^1$H signals of the pyridinyl protons of the other diastereomer (*R*,*S*) (major *sp* conformer) are little affected by the phenyl residue of MPA. We could also deduce from the $^1$H NMR spectrum recorded on the mixture of both diastereomers that the chemical shifts are not depending upon the relative ratio between the two isomers.

Next, we converted the crude mixture of alcohols obtained from the hydrogenation of **4a** carried out in the presence of the precatalyst **2** ($RuCl_2$[(*R*)-DAIPEN][(*R*)-TolBINAP]) into the corresponding (*R*)-MPA esters. The $^1$H NMR spectrum was recorded on the crude mixture of esters obtained after workup (Fig. 2). Taking into account the NMR data reported above, we could deduce an enantiomeric excess of 30% (from integrations of the signals of protons $H^6$ and $H^{6'}$). This result is in good agreement with the enantiomeric excess measured by HPLC (33% ee). The signal of the major isomer in the $^1$H NMR spectrum is observed at lower field than that of the minor diastereomer. We conclude thus that the major ester diastereomer is (*R*,*S*) and thus the (*S*) alcohol is the prevalent enantiomer obtained during hydrogenation of **4a** in the presence of precatalyst **2**. The prevalent alcohol enantiomer obtained from hydrogenations carried out in the presence of precatalysts **1** and **3** is also (*S*) as can be deduced from the HPLC elution order of the major isomer (Table 2).

The same method was then applied to assign the configuration of the other pyridinyl aryl methanol prevalent hydrogenation products **8b**, **8c** and **8d**. In each case, the main enantiomer determined was the alcohol of *S* configuration.

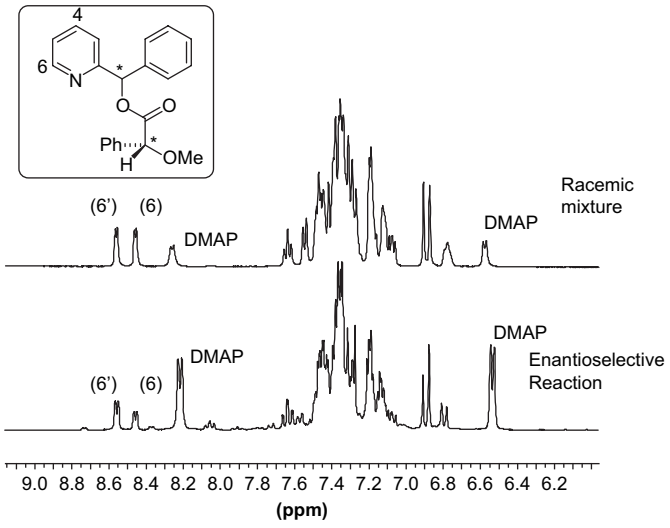



**Figure 2.** Partial $^1$H NMR spectra of **8a** esters obtained from (*R*)-MPA and the crude mixture of alcohols obtained from the hydrogenation of **4a**.

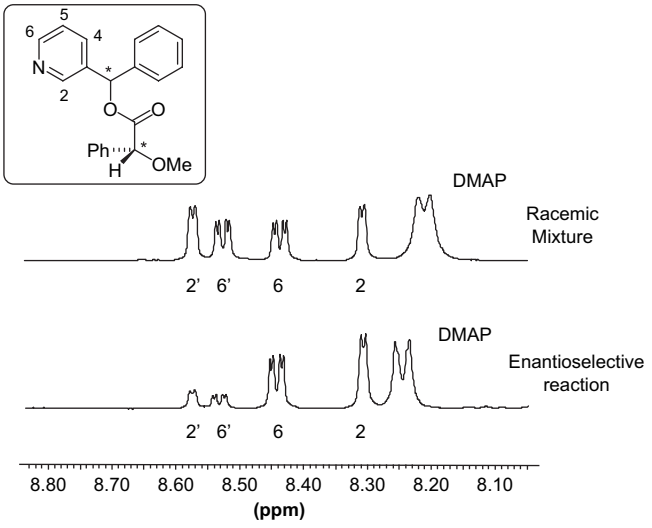



**Figure 3.** Partial $^1$H NMR spectra of (*R*)-MPA esters obtained with crude **9a** isolated from the hydrogenation of **5a**.

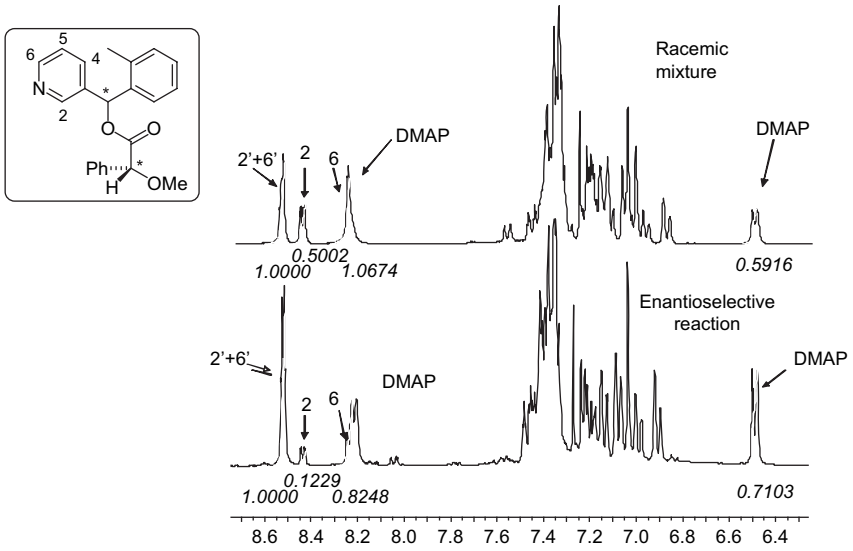



**Figure 4.** Partial $^1$H NMR spectra of **9b** esters resulting from (*R*)-MPA and crude mixture of alcohols obtained from the hydrogenation of **5b**.

In the case of (*R*)-MPA esters obtained from alcohols **9a**–**9c**, the two protons α to the heteroatom ($H^2$ and $H^6$) exhibit characteristic NMR signals as can be seen in Figure 3. Thus, we selected these protons for the determination of the configuration of the major alcohol obtained by asymmetric hydrogenation. The spectrum of the esters prepared from alcohols obtained by hydrogenation of substrate **5a** carried out in the presence of precatalyst **1** shows that the signals of the major diastereomer $H^2$ and $H^6$ are located at higher field that those of the minor one $H^{2'}$ and $H^{6'}$. We can thus infer that the major diastereomer is (*R*,*R*). The alcohol (*R*)-**9a** is thus obtained during hydrogenation of **5a** in the presence of precatalyst **1** with 66% ee as determined by NMR (69% determined by HPLC) (Table 2).

In the case of hydrogenation product **9b**, the configuration attribution is less straightforward because of signal overlapping at low field in the $^1$H NMR spectra. Actually, as can be observed in Figure 4, the signals of protons $H^{2'}$, $H^{6'}$, $H^6$ and those of DMPA are not clearly resolved. However, the comparison of the spectrum recorded on a mixture of diastereomeric esters prepared from the racemic alcohol **9b** and (*R*)-MPA and the spectrum of the mixture of esters prepared with the hydrogenation product of **5b** in the presence of precatalyst **2** and (*R*)-MPA, allowed to

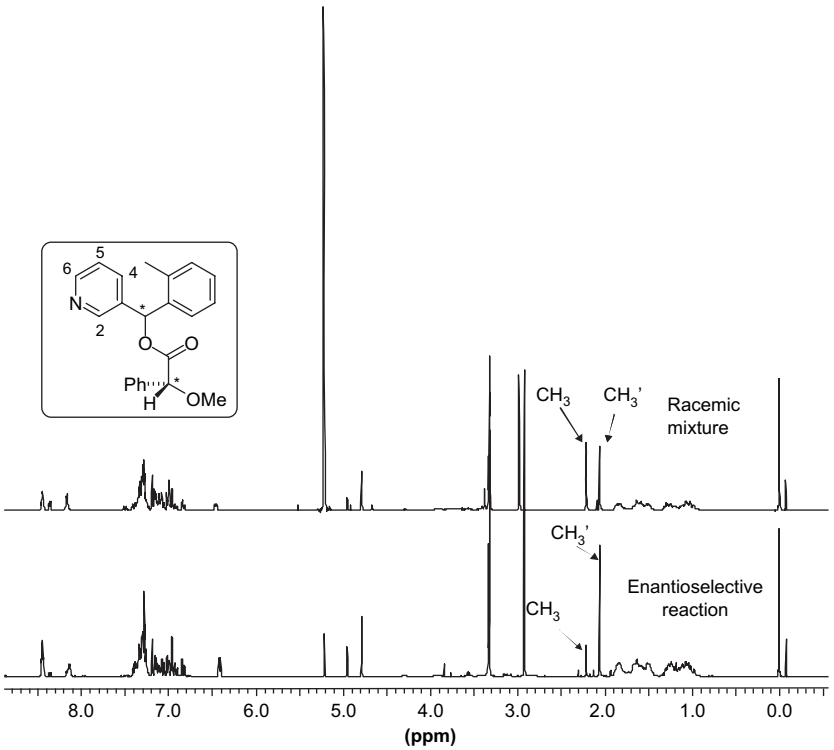



**Figure 5.** $^1$H NMR spectra of **9b** esters resulting from (*R*)-MPA and crude mixture of alcohols obtained from the hydrogenation of **5b**.

assign the signal at $\delta$ 8.55 to $H^{2'}$ and $H^{6'}$, according to the value of the integrations. The major diastereomer prepared from the hydrogenation product **9b** is presenting the main signals at lower field ($H^{2'}$ and $H^{6'}$). This corresponds to a (*R*,*S*) ester diastereomer and thus the (*S*)-**9b** alcohol is the major hydrogenation product.

Moreover, a 73% ee could be calculated from the relative integrations of signals of the diastereomeric esters, which is in good agreement with the ee determined by HPLC (79% ee, precatalyst **2**, Table 2, entry 6). A confirmation of our chirality attribution is provided by the examination of the NMR signals of $CH_3$ protons of the tolyl group of **9b** (Fig. 5). Indeed, the protons of this residue resonate at higher field than those of the minor diastereomer and are thus positioned close to the phenyl group of MPA, which is in agreement with a (*S*) alcohol configuration.

The same approach was used to determine the configuration of the main enantiomer obtained through hydrogenation of the other ketones and the results are summarised in Figure 6. The results obtained using this method are in agreement with the previously published results.[8,10,12]

As it appears from Figure 6, generally, a correlation can be drawn between the (*R*) configuration of the prevalent alcohol enantiomer and the (*R*)-DAIPEN/(*R*)-BINAP chiral auxiliaries combination. However, a remarkable exception is obtained for all the alcohols obtained during the hydrogenation of ketones bearing pyridin-2-yl moieties. The mechanism of hydrogenation of ketones involves a $Rh(H)_2$(diphosphine)(diamine) intermediate (Scheme 7).[15] The diamine ligand plays a critical role in the activity of the catalyst. The hydrogenation is assumed to occur via concomitant transfer of hydrogen atoms from the Ru–H and N–H moieties of the catalytic intermediate. This has been referred to as 'metal-ligand difunctional catalysis'.[6a] This step of transfer of hydrogen atoms determines also the enantioselectivity of the process and consequently the absolute configuration of the major alcohol.[16] According to the way the ketones approaches the catalytic intermediate, the location of the pyridine residue of the ketones on the side of the binaphthyl moiety leads, after transfer of both hydrogen atoms, to the alcohol of (*R*) configuration (Scheme 7). Thus, steric parameters govern the approach of the ketone towards the hydride **A** providing **B** and increasing congestion around the Ru atom going from BINAP to XylBINAP induces higher stereoselectivities. For the pyridin-2-yl ketones, we propose that the ketone approaches differently as the nitrogen atom of the pyridine unit can interact with a hydrogen atom of the second amine via hydrogen bonding stabilising intermediates and leading to the (*S*) alcohol enantiomer (Scheme 7).

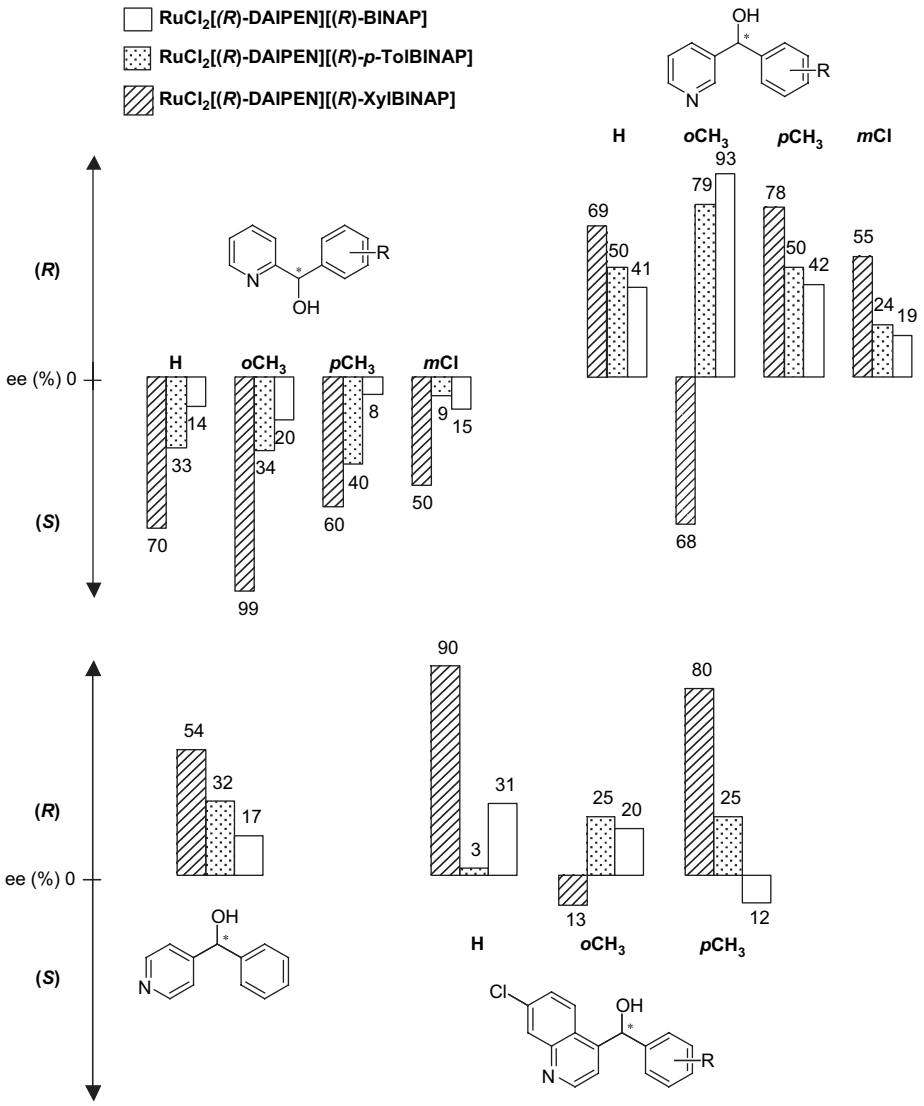
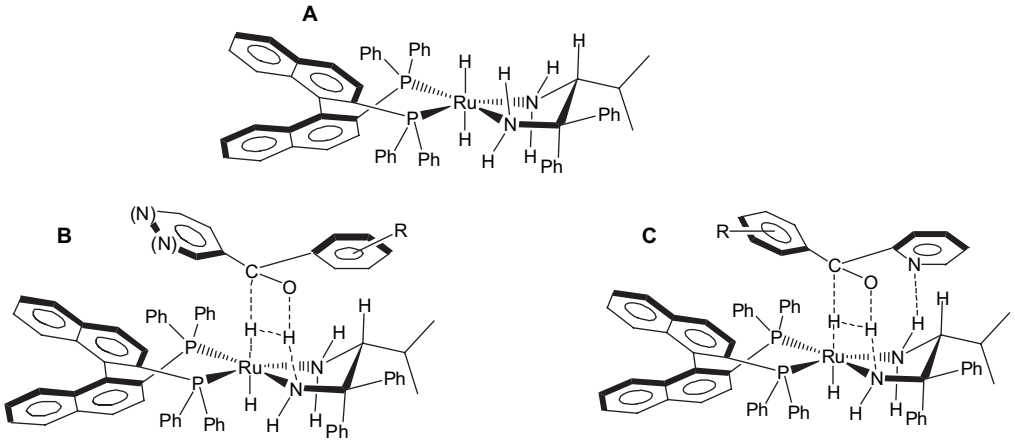



**Figure 6.** Summary of the results on the hydrogenation of pyridyl- and quinolyl-aryl ketones.




**Scheme 7.** Stereochemical models used to explain the formation of the prevalent alcohol enantiomer; A: starting ruthenium dihydride species; B: formation of the (*R*)-alcohol; C: formation of the (*S*)-alcohol.

## 3. Conclusion

This method allows the high yield asymmetric hydrogenation of an array of pyridinyl aryl methanones. The reaction can be carried out with low catalyst loading (S/C up to 1000/1) at relatively low pressure. The use of $RuCl_2$[(*R*)-DAIPEN][(*R*)-XylBINAP] as pre-catalyst provided regularly better enantioselectivities than its counterparts with BINAP or TolBINAP as ligand. Moreover, the enantioselectivity often increased in parallel with the degree of substitution of the diphosphine. However, this trend is not general and catalyst precursors containing BINAP or TolBINAP moiety induced higher enantioselectivities during the hydrogenation of some substrates. In the same way, going from BINAP to XylBINAP, inversion of the configuration of the prevalent enantiomer can be observed sometimes.

## 4. Experimental section

### 4.1. General

NMR spectra were recorded on a AV-300 Bruker spectrometer at 23 °C in $CDCl_3$; chemical shifts are reported in parts per million downfield from TMS and were determined by reference to the residual $^1H$ ($\delta$=7.26) and $^{13}C$ ($\delta$=77.0) solvent signals. All coupling constants are reported in hertz. GLC analyses were performed on a Chrompack CP 9001 apparatus equipped with a flame ionisation detector and a CPSil 5CB (25 m×0.32 mm ID, Chrompack) column. MS and HRMS were performed on a JMS-700m Station mass spectrometer (JEOL) with either electron impact (70 eV) or chemical ($CH_4$) ionisation mode. Melting points are uncorrected. The commercially available $[RuCl_2(C_6H_6)]_2$, (*R*)-DAIPEN, (*R*)-*p*-TolBINAP, (*R*)-XylBINAP and (*R*)-BINAP were purchased from STREM and used as received. *i*-PrOH was distilled over $CaH_2$ under a nitrogen atmosphere. The complexes were prepared according to the literature procedures.[2b] The enantiomeric excesses of the alcohol products were determined by chiral stationary phase HPLC (Daicel Chiralpak AS or AD).

### 4.2. Representative procedure for hydrogenation

In a typical experiment, under nitrogen, a solution of KOH in *i*-PrOH (0.01 M, 500 μL, $5.10^{-6}$ mol) was placed into a Schlenk flask containing the precatalyst ($10^{-6}$ mol) dissolved in *i*-PrOH (1 mL). This solution was transferred to a flask containing the selected ketone (1 mmol) dissolved in *i*-PrOH (1.5 mL). The mixture was then transferred via cannula to an autoclave, which was pressurised with dihydrogen (20 bar). The reaction mixture was stirred vigorously at 30 °C for 15 h. After depressurisation, the solvent was removed under reduced pressure. The residue was then purified by silica gel chromatography (pentane/ether) providing analytically pure alcohols, which were characterised by $^1H$ and $^{13}C$ NMR and MS.

#### 4.2.1. Phenyl(pyridin-2-yl)methanol **8a**

White solid, mp=72 °C, $^1H$ NMR ($CDCl_3$) $\delta$=8.55 (d, 1H, *J*=4.4 Hz, $H^6$), 7.60 (td, 1H, *J*=7.6 and 1.2 Hz, $H^4$), 7.4–7.25 (m, 5H, $H^{o,o'}$, $H^{m,m'}$, $H^p$), 7.20–7.13 (m, 2H, $H^3$ and $H^5$), 5.74 (s, 1H, CHO), 5.6–4.5 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=160.9 ($C^2$), 147.8 ($C^6$), 143.2 ($C^8$), 136.8 ($C^4$), 128.6 ($C^{o,o'}$), 127.8 ($C^p$), 127.1 ($C^{m,m'}$), 122.4 ($C^5$), 121.4 ($C^3$), 75.0 ($C^7$). MS (EI): *m*/*z*=185 ($M^+$, 64), 167 (16), 105 ($M^+$−Py, 35), 79 ($PyH^+$, 100), 77 ($Ph^+$, 72), 51 ($C_4H_3^+$, 35). Optical purity was determined by chiral HPLC on a Chiralpack AD column (*i*-PrOH/hexane: 10:90; flow rate: 0.8 mL/min; detection UV at 215 nm; $t_R$=11 and 14 min). The major enantiomer (*S*) obtained with precatalyst **1** was the first one to be eluted.

#### 4.2.2. Pyridin-2-yl(o-tolyl)methanol **8b**

Yellow oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.57 (d, 1H, *J*=4.5 Hz, $H^6$), 7.60 (m, 1H, $H^4$), 7.26–7.01 (m, 6H, $H^3$, $H^5$, $H^o$, $H^{m,m'}$, $H^p$), 5.97 (s, 1H, CHO), 5.27 (br s, 1H, OH), 2.32 (s, 3H, $H^{14}$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=161.0 ($C^2$), 147.8 ($C^6$), 140.7 ($C^8$), 136.7, 136.2, 130.7, 127.9, 127.7, 126.1, 122.2, 121.1, 72.8 ($C^7$), 19.4 ($CH_3$). Optical purity was determined by chiral HPLC on a Chiralpack AD column (*i*-PrOH/hexane: 4:96; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=20 and 26 min). The major enantiomer (*S*) obtained with precatalyst **1** was the second one to be eluted.

#### 4.2.3. Pyridin-2-yl(p-tolyl)methanol **8c**

Crystalline solid, mp=60°C, $^1H$ NMR ($CDCl_3$) $\delta$=8.55 (d, 1H, *J*=3.9 Hz, $H^6$), 7.60 (m, 1H, $H^4$), 7.26–7.12 (m, 6H, $H^3$, $H^5$, $H^{o,o'}$, $H^{m,m'}$), 5.71 (s, 1H, CHO), 5.5–5.0 (br s, 1H, OH), 2.32 (s, 3H, $CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=161.1, 147.7, 140.3, 137.5, 136.8, 129.2, 127.0, 122.3, 121.3, 74.8 ($C^7$), 21.1 ($CH_3$). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 2:98; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=27 and 32 min). The major enantiomer (*S*) obtained with precatalyst **1** was the first one to be eluted.

#### 4.2.4. (3-Chlorophenyl)(pyridin-2-yl)methanol **8d**

Yellow oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.56 (d, 1H, *J*=4.5 Hz, $H^6$), 7.67 (t, 1H, *J*=6.9 Hz, $H^4$), 7.45–6.99 (m, 6H, $H^3$, $H^5$, $H^{o,o'}$, $H^m$, $H^p$), 5.71

(s, 1H, CHO), 5.4–5.2 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=159.7, 147.5, 144.8, 136.5, 134.0, 129.3, 127.4, 126.6, 124.7, 122.2, 120.8, 73.9 ($C^7$). Optical purity was determined by chiral HPLC on a Chiralpack AD column (*i*-PrOH/hexane: 7:93; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=14 and 19 min). The major enantiomer (*S*) obtained with precatalyst **1** was the second one to be eluted.

*4.2.5. Phenyl(pyridin-3-yl)methanol* ***9a***

White solid, mp=66 °C, $^1H$ NMR ($CDCl_3$) $\delta$=8.43 (s, 1H, $H^2$), 8.29 (d, 1H, *J*=3.9 Hz, $H^6$), 7.67 (d, 1H, *J*=7.3 Hz, $H^4$), 7.35–7.20 (m, 5H, $H^{o,o'}$, $H^{m,m'}$, $H^p$), 7.18 (m, 1H, $H^5$), 5.8 (s, 1H, CHO), 5.3–4.0 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=148.0, 147.8, 143.2, 139.9, 134.5, 128.6, 127.8, 126.5, 123.5, 73.7 ($C^7$). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 8:92; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=21 and 25 min). The major enantiomer (*R*) obtained with precatalyst **1** was the second one to be eluted.

*4.2.6. Pyridin-3-yl(o-tolyl)methanol* ***9b***

Yellow oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.42 (s, 1H, $H^2$), 8.33 (d, 1H, *J*=3.9 Hz, $H^6$), 7.60 (d, 1H, *J*=7.8 Hz, $H^4$), 7.45 (m, 1H, $H^5$), 7.25–7.12 (m, 4H, $H^o$, $H^{m,m'}$, $H^p$), 5.98 (s, 1H, CHO), 4.20–4.00 (br s, 1H, OH), 2.20 (s, 3H, $CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=148.5, 148.2, 140.8, 138.8, 135.2, 134.8, 130.7, 127.8, 126.4, 126.3, 123.4, 70.9 ($C^7$), 19.3 ($CH_3$). MS (EI): *m*/*z*=199 ($M^+$, 3), 180 (100), 108 ($M^+$−Tol, 21), 91 ($Tol^+$, 36), 78 ($Py^+$, 17), 77 ($Ph^+$, 11), 51 ($C_4H_3^+$, 11). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 5:95; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=28 and 32 min). The major enantiomer (*S*) obtained with precatalyst **1** was the first one to be eluted.

*4.2.7. Pyridin-3-yl(p-tolyl)methanol* ***9c***

Yellow pale solid, mp=132 °C, $^1H$ NMR ($CDCl_3$) $\delta$=8.45 (s, 1H, $H^2$), 8.32 (d, 1H, *J*=3.9 Hz, $H^6$), 7.67 (d, 1H, *J*=7.3 Hz, $H^4$), 7.19–7.13 (m, 5H, $H^5$, $H^{o,o'}$, $H^{m,m'}$), 5.77 (s, 1H, CHO), 4.2–3.6 (br s, 1H, OH), 2.32 (s, 3H, $CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=148.0, 147.7, 140.2, 137.65, 134.4, 129.6, 129.3, 126.5, 123.4, 73.6 ($C^7$), 21.0 ($CH_3$). MS (EI): *m*/*z*=199 ($M^+$, 64), 184 ($M^+$−Me, 82), 167 ($M^+$−Me−OH, 35), 119 (23), 108 ($M^+$−Tol, 37), 106 (100), 93 (49), 91 ($Tol^+$, 99), 80, 78 ($Py^+$, 58), 77 ($Ph^+$, 36), 51 ($C_4H_3^+$, 28). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 4:96; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=48 and 55 min). The major enantiomer (*R*) obtained with precatalyst **1** was the second one to be eluted.

*4.2.8. (3-Chlorophenyl)(pyridin-3-yl)methanol* ***9d***

Yellow oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.5 (s, 1H, $H^2$), 8.42 (d, 1H, *J*=4.8 Hz, $H^6$), 7.67 (d, 1H, *J*=7.9 Hz, $H^4$), 7.38 (br s, 1H, $H^5$), 7.26–7.22 (m, 4H, $H^{o,o'}$, $H^m$, $H^p$), 5.81 (s, 1H, CHO), 5.27 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=148.4, 147.7, 145.1, 139.3, 134.6, 134.5, 129.9, 128.0, 126.6, 124.6, 123.7, 73.2 ($C^7$). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 10:90; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=20 and 24 min). The major enantiomer (*R*) obtained with precatalyst **1** was the second one to be eluted.

*4.2.9. Phenyl(pyridin-4-yl)methanol* ***10a***

White solid, mp=125 °C, $^1H$ NMR ($CDCl_3$) $\delta$=8.21 (d, 2H, *J*=4.9 Hz, $H^2$, $H^6$), 7.29–7.25 (m, 7H, $H^3$, $H^5$, $H^{o,i'}$, $H^{m,m'}$, $H^p$), 5.8–5.3 (br s, 1H, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=153.7, 148.9, 147.0, 143.0, 128.9, 128.6, 127.9, 126.8, 126.7, 122.6, 121.4, 74.5 ($C^7$). MS (EI): *m*/*z*=185 ($M^+$, 64), 167 (16), 105 (35), 79 ($Py^+$, 100), 77 ($Ph^+$, 72), 51 ($C_4H_3^+$, 35). Optical purity was determined by chiral HPLC on a Chiralpack AD column (*i*-PrOH/hexane: 3:97; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=86 and 94 min). The major enantiomer (*R*) obtained with precatalyst **1** was the first one to be eluted.

*4.2.10. (7-Chloroquinolin-4-yl)(phenyl)methanol* ***11a***

Oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.83 (d, 1H, *J*=4.2 Hz, $H^2$), 8.03 (d, 1H, *J*=2.0 Hz, $H^8$), 7.85 (d, 1H, *J*=9.1 Hz, $H^5$), 7.69 (m, 1H, $H^6$), 7.38–7.26 (m, 6H, $H^3$, $H^{o,o'}$, $H^{m,m'}$, $H^p$), 6.42 (s, 1H, CHO), 3.9–3.4 (br s, 1H, OH). MS (EI): *m*/*z*=268 ($M^+$, 12), 253 (100), 196 (12), 91 ($Tol^+$, 8). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 5:95; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=32 and 38 min). The major enantiomer (*R*) obtained with precatalyst **1** was the second one to be eluted.

*4.2.11. (7-Chloroquinolin-4-yl)(o-tolyl)methanol* ***11b***

Oil, $^1H$ NMR ($CDCl_3$) $\delta$=8.91 (d, 1H, *J*=4.4 Hz, $H^2$), 8.13 (d, 1H, *J*=1.95 Hz, $H^8$), 7.70 (d, *J*=9.0 Hz, 1H, $H^5$), 7.58 (d, 1H, *J*=4.4 Hz, $H^3$), 7.41 (dd, 1H, *J*=7.1 and 2.2 Hz, $H^6$), 7.26–7.02 (m, 4H, $H^o$, $H^{m,m'}$, $H^p$), 2.51 (s, 3H, $CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=151.4, 136.0, 131.1, 129.1, 128.6, 127.7, 127.1, 126.6, 125.1, 119.1, 64.4, 41.4 ($CH_3$). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 5:95; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=24 and 31 min). The major enantiomer (*S*) obtained with precatalyst **1** was the first one to be eluted.

*4.2.12. (7-Chloroquinolin-4-yl)(p-tolyl)methanol* ***11c***

$^1H$ NMR ($CDCl_3$) $\delta$=8.77 (d, 1H, *J*=4.1 Hz, $H^2$), 7.97 (d, 1H, *J*=1.5 Hz, $H^8$), 7.80 (d, *J*=9.0 Hz, 1H, $H^5$), 7.70 (d, 1H, *J*=4.4 Hz, $H^3$), 7.32 (dd, 1H, *J*=9.3 and 1.7 Hz, $H^6$), 7.27–7.17 (m, 4H, $H^{o,o'}$, $H^{m,m'}$), 6.37 (s, 1H, CHO), 3.5–3.3 (s, 1H, OH), 2.29 (s, 3H, $CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$=151.1, 149.2, 148.3, 138.9, 138.3, 135.0, 129.6 ($C^{o,o'}$), 128.5, 127.5, 127.2 ($C^{m,m'}$), 125.4, 124.1, 118.5, 72.4 ($C^{11}$), 21.1 ($CH_3$). Optical purity was determined by chiral HPLC on a Chiralpack AS column (*i*-PrOH/hexane: 5:95; flow rate: 0.7 mL/min; detection UV at 215 nm; $t_R$=29 and 41 min). The major enantiomer (*R*) obtained with precatalyst **1** was the second one to be eluted.

### 4.3. Representative procedure for esterification

In a typical experiment, the alcohol (0.1 mmol) was dissolved in dichloromethane (3 mL) along with (*R*)-MPA (0.183 g, 0.11 mmol), DMAP (0.0021 g, 0.012 mmol), and DCC (0.0416 g, 0.2 mmol) in a Schelnk tube under nitrogen. The mixture is stirred for 15 h at room temperature. Then, the solvent was removed under reduced pressure. The residue was then either directly analysed by NMR or purified by silica gel chromatography (pentane/ether) to give the analytically pure ester products.

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