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Asymmetric hydroamination of acrylonitrile derivatives catalyzed by Ni(II)-complexes

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ABSTRACT

Chiral ferrocenyl tridentate phosphine ligands were synthesized and used in asymmetric hydroamination reactions catalyzed by Ni(II)-complexes. Compounds of the type $[Ni(PPP)L]^{2+}$, where L is a chloride, solvent molecule or a coordinated substrate, were isolated. The efficiency of these complexes in asymmetric catalysis was high when aliphatic or aromatic amines were reacted with electron-poor olefins, especially with acrylonitrile derivatives. This hydroamination reaction affords up to 95% enantioselectivity at −80 °C for the addition of morpholine to methacrylonitrile (69% ee at room temperature).

1. Introduction

The most useful application of organometallic chemistry is the development of new catalysts for the synthesis of organic compounds. The use of organometallic compounds in order to catalyze asymmetric heterofunctionalization reactions is a very important goal for the synthesis of fine products.[1] Hydroamination is an interesting and economical process that can be used to build, without side products, secondary or tertiary amines, starting from the direct addition of amines to olefins.[2,3] From an industrial point of view, the catalytic hydroamination reaction is very interesting, because of the use of a large number of secondary and tertiary amines as active components in drugs and agrochemicals. Moreover, an asymmetric approach is particularly attractive, because chiral amines are valuable.[4] Access to synthetic routes that lead efficiently to enantiomerically pure material is becoming increasingly important.[3] In fact, the asymmetric hydroamination of alkenes, catalyzed by transition metals, is one of the research fields that to date has not found a general solution for industrial applications. Currently, catalysts that allow the formation of enantiomerically pure hydroamination products are rare.[5] These are based principally on lanthanide and group 4-catalysts, useful for cyclization reactions,[6] and on late transition metals for intermolecular reactions.[7] Recently, remarkable advances were made with the addition of amines to Michael-acceptors, resulting in high yields and high asymmetric induction.[8–10] The achiral addition of amines to α,β-unsaturated nitriles was pioneered by Trogler et al.[11] They investigated palladium(II)-complexes as catalysts in the addition of protonated aniline $[NH_3Ph][BPh_4]$ to acrylonitrile and its derivatives. When the reaction is carried out with aniline instead of the ammonium salt, at least 1 equiv of NH_3Ph^+ must be added to the substrates, since a proton source is a required co-catalyst. The most active catalyst (TON up to 44) is a cationic palladium(II) complex containing a tridentate bis(phosphine), that is, a pincer-type ligand.[†]

Following ab initio theoretical studies,[12] we decided to use chiral nickel(II) complexes to catalyze the addition of primary or secondary amines to acrylonitrile derivatives. Only a few examples of the nickel-catalyzed enantioselective hydroamination reactions are known.[10,13] Recently, we published preliminary results of the asymmetric addition of aromatic and aliphatic amines to electron-poor olefins catalyzed by Ni(II)-complexes with chiral triphosphine ferrocenyl ligands.[14] The addition of secondary amines to the acrylonitrile derivatives also permitted the synthesis of β-amino acids,[15] and when the catalysis was performed in ionic liquids, the activity of the cationic catalyst improved (TON up to 300) and the chiral catalysts could be reused.[16]

Herein, we report improvements to the scope and limitations of the addition of aliphatic and aromatic amines to acrylonitrile derivatives, catalyzed by Ni(II)-complexes with chiral ferrocenyl tridentate ligands such as (*R,S*)-Pigiphos.

2. Results and discussion

According to the preliminary results,[14] $[Ni((R,S)\text{-Pigiphos})(L)]^{2+}$ **1b–c** (where L = THF or CH_3CN, Scheme 1) catalyzed the hydroamination reaction of aliphatic and aromatic amines and acrylonitrile derivatives producing good–excellent yield. The

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† (1,5-Bis-(di-*tert*-butylphosphino)pentan-3-yl)methyl palladium(II) = [Pd(X)-(PCP)]+.

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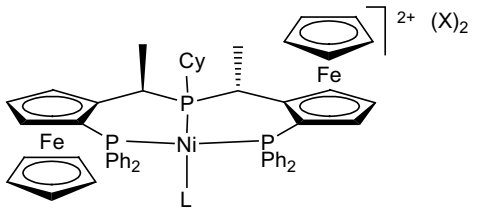


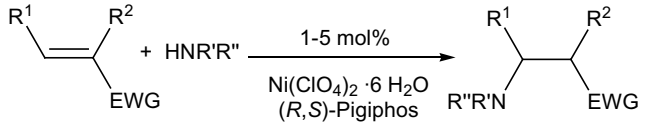
1b-c

Scheme 1. Ni(II)-catalysts **1b–c** [Ni((*R*,*S*)-Pigiphos)L](X)$_2$ for the hydroamination reactions. L = THF (**1b**) or CH_3CN (**1c**). X = ClO_4^-.

hydroamination reaction of morpholine and methacrylonitrile produced excellent yield, and the Ni^{2+}-complex could be used as an isolated complex or as formed in situ (from $Ni(ClO_4)_2{\cdot}6H_2O$ and (*R*,*S*)-Pigiphos as a ligand), without affecting the catalytic activity under the same conditions. [NiCl((*R*,*S*)-Pigiphos)](PF_6) **1a** (also characterized by single-crystal X-ray analysis)[17] is inactive in the hydroamination catalysis. We suspected that the complexes might show activity in these hydroamination reactions if the fourth coordination site was accessible due to the potential lability of the chloride ligand. However, this was not the case. In this context, a common strategy was the abstraction of the chloride in the presence of a weakly coordinating ligand such as CH_3CN or THF.

In order to identify the scope of these Ni(II) catalysts with respect to the substrates, a colorimetric screening using simple spot tests was used, monitoring the presence of the primary or secondary amines employed.[18] The addition of aliphatic and/or aromatic amines (such as derivatives of aniline, ethylamine, cyclohexylamine, diethylamine, or diphenylamine) to styrene or norbornene with Ni(II) catalysts showed only trace amounts of products (maximum isolated yield 31.4%),[17] and almost no enantioselectivity was detected. The Ni(II)-compounds with triphosphine ligands catalyzed almost only the addition of cyclic secondary amines to acrylonitrile. If primary aliphatic amines are used, only trace amounts of the hydroamination products and no enantioselectivities were detected. Furthermore, we found that the order of the addition of the substrates to the reaction mixture affects the catalyst's performance. The activity and the enantioselectivity decreased dramatically if the amine (aliphatic or aromatic) is added to the catalyst before the olefin. The formation of [Ni((*R*,*S*)-Pigiphos)(olefin)]$^{2+}$ appears to be a key step in the catalytic cycle (vide infra). Excess of the amine and resulting coordination of the amine to the Ni(II)-complex appear to form catalytically inactive species.

In the case of methacrylonitrile the excellent yield was combined with a promising enantioselectivity.[14] Encouraged by these results, attention was extended to other aliphatic secondary amines, in particular piperidine, thiomorpholine, piperazine and derivatives, and their catalytic addition to activated olefins was investigated (Scheme 2). The catalytic activities were as high as those for the addition of morpholine to methacrylonitrile. Table 1 summarizes the results obtained for reactions of aliphatic amines with acrylic acid derivatives. Using 5 mol % catalyst, the addition of aliphatic amines to crotonitrile, methacrylonitrile, methyl acrylate,



R^1, R^2 = H, Me
EWG = CN, COOR (R = Me, Et, H)

Scheme 2.

Table 1
Hydroamination reaction with aliphatic amines catalyzed by [Ni((*R*,*S*)-Pigiphos)(THF)](ClO_4)$_2$ formed in situ[a]

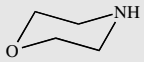
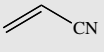
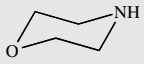
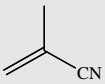
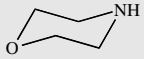
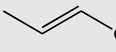
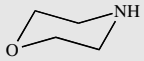
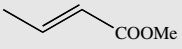
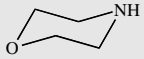
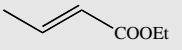
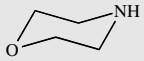
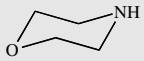
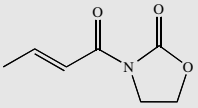
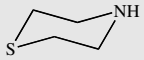
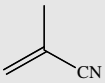
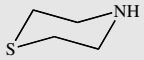
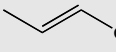
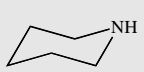
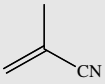
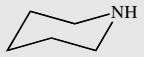
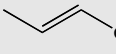
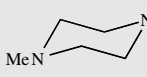
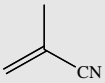
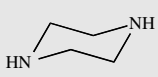
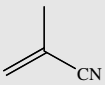
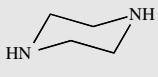
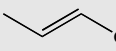
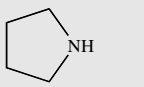
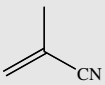
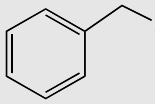
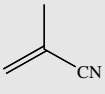
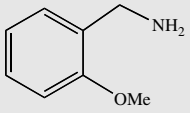
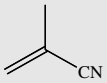
Entry	Amine	Olefin	Yield[b] (%)	ee[c] (%)
1			99	
2			99	69
3			99	3
4			63	*rac*
5			77	*rac*
6			70	
7			99	*rac*
8			99	61
9			62	10
10			98	65
11			85	7
12			84	37
13			73[d,e] 65[f,e] + 27[f,g]	n.d. 38
14			65[h]	n.d.
15			90	*rac*
16			5	5

Table 1 (*continued*)

Entry	Amine	Olefin	Yield[b] (%)	ee[c] (%)
17			45	4

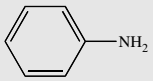
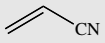
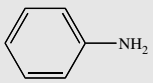
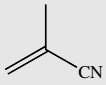
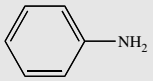
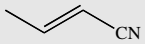
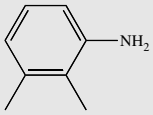
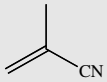
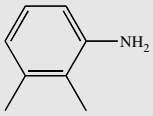
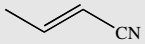
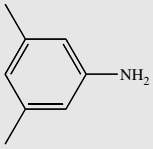
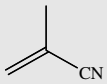
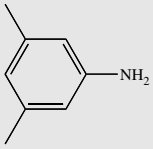
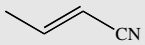
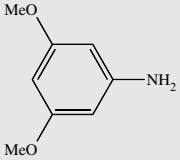
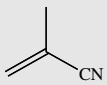
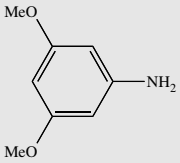
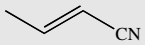
[a] Reactions in THF, under inert conditions, 24 h, rt, 5 mol % cat.
[b] Yields are for isolated material after extraction and flash chromatography.
[c] Enantioselectivity determined by GC analysis or HPLC analysis.
[d] Olefin/amine = 2:1.
[e] Double intramolecular hydroamination, yielding *N*,*N*′-bis-(2-nitrilopropyl)-piperazine.
[f] Olefin/amine = 1:1.
[g] Single hydroamination reaction, yielding 2-methyl-3-(*N*-piperazinyl)-propanenitrile.
[h] Double intramolecular hydroamination, yielding *N*,*N*′-bis-(1-methyl-2-nitrilo-ethyl)-piperazine.

and methyl or ethyl crotonate afforded good to excellent isolated yields of the products. These experiments were carried out in THF, for 24 h at room temperature (S/C = 20). The most significant example is still represented by the hydroamination of methacrylonitrile with morpholine, which produced a quantitative yield of the product at 69% ee (Table 1, entry 2). Thiomorpholine or piperidine gave quantitative isolated yields and enantioselectivities greater than 60% ee (entries 8 and 10). Crotonates and oxazolidinones (used by Jørgensen and Hii for their asymmetric hydroamination reactions)[9,10] added morpholine quite effectively, however, no chiral induction was observed (entries 4–7). We found that the asymmetric induction is significant only for methacrylonitrile, where the newly formed stereogenic center is α to the nitrile group. Although crotonitrile formed good yields of the product 3-(morpholin-4-yl)butanenitrile, the enantioselectivity was either low (at most 10% ee) or the product was racemic. The use of pyrrolidine as an amine gave high activity (90% yield) but poor enantioselectivity (Table 1, entry 15), as well as the addition of benzylamine (5% yield, entry 16, usefull for the synthesis of an unprotected β-aminoacid)[15] or of the more electron-rich *o*-methoxybenzylamine (45% yield, entry 17) gave only low to moderate yields with very low enantioselectivities. The addition of acyclic secondary amines such as diphenylamine gave only trace amounts of the hydroamination products (<10% yield), without significant enantioselectivity.

In the less nucleophilic aromatic amines, the Ni catalyst also showed relatively high activities, with TON up to 70 for the addition of aniline to crotonitrile, and moderate to high isolated yields of the hydroamination product (Table 2).

However, there were large effects on the outcome of the catalytic reaction due to the substituents on the arene of the aromatic amine. In particular, *ortho*-substituents were detrimental to high catalytic activity, probably for steric reasons (entries 4 and 5). Strong electron-releasing substituents, such as in 3,5-dimethoxyaniline, produced slightly increased yields (entries 8 and 9) compared to methyl groups in the same position (entries 6 and 7). On the other hand, the reaction of 3,5-bis(trifluoromethyl)aniline with different cyanoolefins gave only starting materials under the same conditions. The activities observed for the Ni catalyst were comparable to or better than those previously reported for Pd catalysts,[19] for which generally higher temperatures and longer reaction times are required. However, the enantioselectivities obtained were generally low, and for the substrate combinations in Table 2 reached only ca. 24% ee. While the presence of a source of H^+ was necessary for previously reported systems based on Pd(II) catalysts,[11,20] in the case of the Ni-catalyzed reaction, the addition of TfOH or ammonium salts led to complete catalyst deactivation and only trace amounts of products were detectable.

Table 2
Hydroamination reaction with aromatic amines catalyzed by [Ni((*R*,*S*)-Pigiphos)(THF)]$(ClO_4)_2$ formed in situ[a]

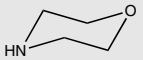
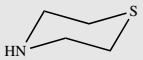
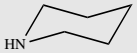
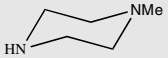
Entry	Amine	Olefin	Yield[b] (%)	ee[c] (%)
1			99	
2			85	18.1
3			81	22.7
4			26	24.1
5			35	17.9
6			52	8.3
7			69	17.6
8			62	n.d.
9			78	n.d.

[a] Reactions in THF, under inert conditions, 24 h, rt, 5 mol % cat.
[b] Yields are for isolated material after extraction and FC.
[c] Enantioselectivity determined by GC analysis or HPLC analysis.

The hydroamination catalysis with aniline and acrylate derivatives (methyl- and ethyl-crotonate and methyl-, and ethyl-methacrylate) gave isolable products only for methylacrylate (17% yield). In the other cases, only trace amounts of the products were detectable by GC–MS analysis.

Furthermore, the effect of temperature was studied for the catalytic addition of aliphatic cyclic amines to methacrylonitrile (Table 3). As expected, at 50 °C the reaction was faster, with 75% conversion after 5 h, but poorer enantioselectivity. At 0 °C the enantioselectivity was increased to 71% ee (entry 3). The optimized temperature was −80 °C, where the enantioselectivity reached the maximum value of 95% ee for the addition of morpholine to methacrylonitrile (entry 6, after 48 h) and 96% ee for the addition of *N*-methylpiperazine to methacrylonitrile (entry 22), reflecting a typical positive effect of low temperatures on the Lewis-acid

Table 3
Hydroamination reaction with methacrylonitrile and aliphatic cyclic amines catalyzed by 5% [Ni(*Pigiphos*)(solvent)]$(ClO_4)_2$ (isolated and in situ)

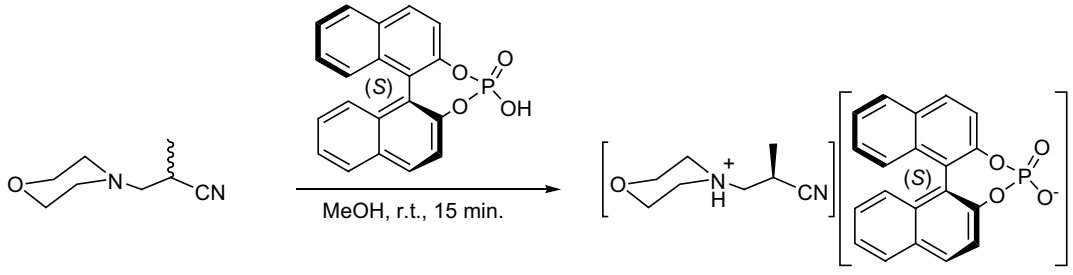
Entry	Amine	Catalyst	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1		**1b**	50	24	99	54
2		**1b** in situ[a]	25	24	99	69
3		**1b**	0	24	99	71
4		**1b**	−25	24	99	85
5		**1b** in situ[a]	−50	24	98	90
6		**1b**	−80	48	84	95
7		**1c**	−80	48	90	91
8		**1b** in situ[a]	−80	48	88	92
9		**1b**	−78 to rt	24	60	91
10		**1b** in situ	25	24	99	61
11		**1b** in situ	−50	24	85	83
12		**1b**	−80	48	82	91
13		**1c**	−80	48	96	90
14		**1b** in situ	−80	48	87	89
15		**1b** in situ	25	24	98	65
16		**1b** in situ	−50	24	77	76
17		**1b**	−80	48	69	92
18		**1c**	−80	48	83	90
19		**1b** in situ	−80	48	86	88
20		**1b** in situ	25	24	84	37
21		**1b** in situ	−50	24	82	82
22		**1b**	−80	48	68	96
23		**1c**	−80	48	83	91
24		**1b** in situ	−80	48	85	89

[a] Reactions under inert conditions, 5 mol % cat.
[b] Yields are for isolated material after extraction and FC.
[c] Enantioselectivity determined by GC analysis with chiral columns (β-dex, γ-dex).

activation of substrates.[21] Interestingly, the reactions catalyzed by the Ni(II)-complex formed in situ had similar activities but lower enantioselectivities (Δ = 1–7% ee) than the hydroamination catalyzed by the isolated [Ni(*Pigiphos*)(THF)]$^{2+}$, whereas the use of [Ni(*Pigiphos*)$(NCCH_3)$]$^{2+}$ as a catalyst demonstrated comparable activities but also lower asymmetric induction (Δ = 1–4% ee, entries 7, 13, 18, and 23). Marks et al. also reported that low temperatures significantly improved the enantioselectivity in the asymmetric hydroamination/cyclization of 2,2-dimethyl-1-aminopent-4-ene. In the cyclization, the highest enantioselectivity of 74% ee was achieved at −30 °C (53% ee at room temperature).[22] In the hydroamination of methacrylonitrile with morpholine catalyzed by [Ni(*Pigiphos*)(THF)]$(ClO_4)_2$, the best result combining both activity and selectivity was obtained at −50 °C, with >99% yield and 90% ee (after 24 h). When the reaction was carried out at −78 °C and the solution was allowed to warm slowly to room temperature, 60% yield and 91% ee were observed after 24 h (entry 9). This procedure represents an important technical improvement, which allows the use of a cryostat to be avoided, and represents one of the rare examples of an asymmetric catalytic hydroamination reaction that has good activity and excellent enantioselectivity. Similar observations were also made in the asymmetric hydrophosphination reactions of methacrylonitrile catalyzed by the same [Ni(*Pigiphos*)(solvent)]$^{2+}$ complexes. The 65% ee detected at room temperature (24 h, in methacrylonitrile) could be improved up to 90% ee at −20 °C and at −40 °C.[23,24]

Although the racemic products of the addition of aliphatic or aromatic amines to methacrylonitrile or crotonitrile were reported in the pioneering studies of Trogler, to the best of our knowledge, the absolute configurations of the two enantiomers have not been described. Importantly, a credible mechanistic proposal must include a rationalization of the absolute configuration of the major enantiomer. Thus, it was essential to determine the absolute configuration of the major enantiomers of our catalysis products. We attempted to achieve this goal by the resolution of the mixture of enantiomers by the formation of a diastereomeric mixture, the product of the reaction between the catalysis products with enantiomerically pure, chiral binaphthyl derivatives. The enriched 2-methyl-3-(morpholin-4-yl)propanenitrile reacts with (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate,[24] yielding solid **2a** (Scheme 3). Crystallization by slow diffusion of diethyl ether into an ethanol solution of the product yielded X-ray quality crystals. The single-crystal X-ray analysis permitted the assignment of the absolute configuration of (−)-2-methyl-3-(*N*-morpholin-4-yl)propanenitrile as (*R*). A distance of 1.628(2) Å between the ammonium hydrogen bond and one of the oxygen atoms of the phosphate fragments indicates the presence of a strong hydrogen bridge in the solid state (Fig. 1).

The basic hydrolysis confirmed that the major product of the hydroamination catalysis is the (*R*)-product. In the chiral GC (β-



Scheme 3.

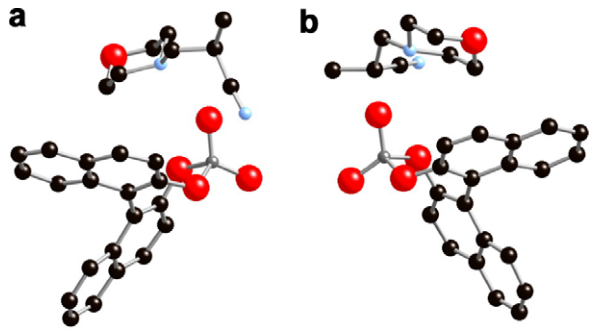


Figure 1. Representation of the X-ray structure of (a) (+)-[2-(*R*)-methyl-3-(morpholinium)-propanenitrile][(*S*)-1,1′-binaphthyl-2,2′-diylphosphate] **2a** and (b) (−)-[2-(*R*)-methyl-3-(morpholinium)-propanenitrile][(*R*)-1,1′-binaphthyl-2,2′-diylphosphate], **2b**. Hydrogen atoms and solvent are omitted for clarity. Illustration generated using *CrystalMaker*®.

dex, 92 °C iso), the extracted product displayed only one peak with a retention time of 139.2 min, corresponding to the major enantiomer from the catalytic reaction. It should be noted that the salt was obtained in 80.9% yield starting from an enantioenriched sample of the amine with an er of 82:18, indicating an almost quantitative crystallization of the major (*R*)-enantiomer. Our attempts to isolate the minor (*S*)-enantiomer from the same mixture were unsuccessful. The mixture of enantiomers was therefore reacted with the opposite enantiomeric acid (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, under the same conditions as mentioned above, yielding 14.6% of crystals also suitable for an X-ray diffraction study. The inverse specific rotation {$[\alpha]_D$ = −337.3 (*c* 1, CH_2Cl_2) for **2b** vs $[\alpha]_D$ = +335.2 (*c* 1, CH_2Cl_2) for **2a**} is mainly due to the inverse configuration of the binaphthyl group, since the absolute configuration of the morpholinium cation was still (*R*) (Fig. 1b). These results were confirmed by hydrolysis of the salt, which yielded the pure major (*R*)-enantiomer, as in the previous experiment.

3-(*N*-Phenylamino)-butyronitrile, the product of the reaction of aniline and crotonitrile (18% ee), was also reacted with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate to give single crystals suitable for X-ray diffraction of the corresponding (*R*)-anilinium salt ($[\alpha]_D$ = −204.2, *c* 1 in CH_2Cl_2, Fig. 2). A short NH^+–O contact of 1.7391(3) Å was also found. The basic hydrolysis of

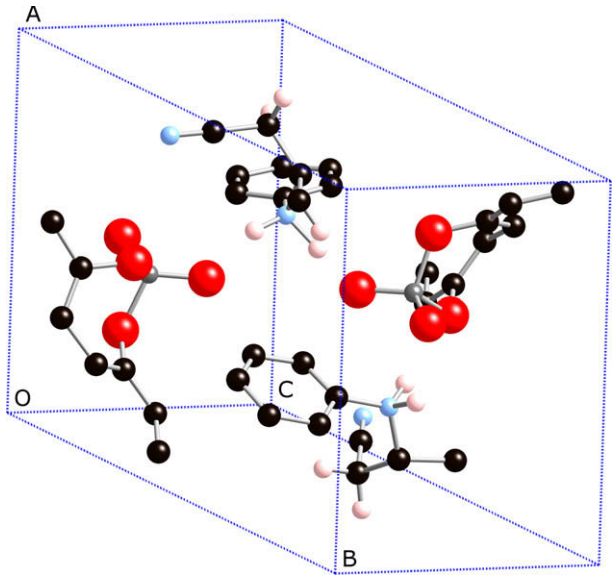


Figure 2. Unit cell view of 3-(*R*)-(phenylammonium)butanenitrile (*R*)-(−)-1,1′-binaphthyl-2,2′-diylphosphate **3**. Most hydrogen atoms are omitted for clarity. Illustration generated using *CrystalMaker*®.

the salt and HPLC analysis confirmed that the major enantiomer of the catalytic reaction had the (*R*)-absolute configuration.

Using these results, it is possible to assign the absolute configuration for other hydroamination products by analogy. Thus, for the (*R,S*)-Pigiphos Ni(II)-catalyzed addition of morpholine, thiomorpholine, piperidine, and (*N*)-methylpiperazine to methacrylonitrile, the absolute configuration of the hydroamination products was (*R*). The specific rotation of the enantiomerically enriched products was always negative.

Regarding a possible catalytic cycle, the hydroamination reactions catalyzed by [Ni((*R,S*)-Pigiphos)(THF)]$^{2+}$ complexes appear to be similar to the reported hydrophosphination mechanism.[23] Reaction of $Ni(ClO_4)_2{\cdot}6H_2O$ and (*R,S*)-Pigiphos in methacrylonitrile gives [Ni((*R,S*)-Pigiphos)(NC–C(Me)=CH_2)]$^{2+}$.[24] This compound was then isolated. The X-ray structure revealed that the (*R,S*)-*Pigiphos* ligand is coordinated η^3 to the nickel center and that the methacrylonitrile is coordinated η^1 through the nitrile nitrogen.[23,24] This complex is an active catalyst for the enantioselective hydroamination of methacrylonitrile with morpholine and yields the product in similar enantiomeric excess as the in situ generated catalyst (67% ee, in THF, at room temperature). Thus, the complex is a likely intermediate in the catalytic cycle for the enantioselective hydroamination of methacrylonitrile. Additionally, investigation of the asymmetric hydroamination of other vinyl cyanide derivatives, such as *cis*-2-pentenylnitrile and *trans*-cinammonitrile, revealed that the enantioselectivities of these reactions were low and reached a maximum of 14% ee. Moreover, the addition of the amine to [Ni(((*R,S*)-Pigiphos)(THF)]$(ClO_4)_2$ rendered the catalyst less active and less selective. This is probably due to the formation of a Ni–amido complex, which is incapable of catalyzing the hydroamination reaction, and in some cases, no products were detected at all. Therefore, the interaction of the [Ni(((*R,S*)-Pigiphos)]$^{2+}$ species and amine seems to be a competitive deactivation pathway that may be responsible for the lower activity (and selectivity) of the catalysis.

The mechanism for C=C activation[12] might involve an equilibrium between η^1 nitrile coordination and η^2 olefin coordination to the Ni center. The stereoselective step would be the nucleophilic anti-Markovnikov attack on the olefin. It should be noted that this cycle requires the formation of a tertiary carbon bound to the crowded nickel center. The addition of the amine should proceed to give the anti-Markovnikov product, and for methacrylonitrile the stereocenter in the product is adjacent to the cyano group, at the α-position to the Ni-center. The α-cyanoalkyl intermediate could also undergo β-hydrogen elimination, generating the corresponding cyanoenamine, which was, however, never detected experimentally.

The low enantiomeric excess of the products deriving from crotonitrile, pentenylnitrile or cinnamonitrile suggests that the stereochemistry-determining step of the hydroamination catalytic cycle is *not* the nucleophilic attack of morpholine on the olefin. This conclusion also implies that the mechanism for these hydroamination reactions does not involve metal–carbon bond formation and proceeds strictly via a classical Lewis acid substrate activation followed by 1,4-addition of the amine N–H bond, forming an unusual ketenimine intermediate.[22] Therefore, the enantioselectivity in the hydroamination of methacrylonitrile should derive from an asymmetric proton-transfer step, similar to the cycle proposed for the hydrophosphination reactions of acrylonitrile derivatives, catalyzed by the same [Ni(((*R,S*)-Pigiphos)(THF)]$(ClO_4)_2$.[23]

3. Conclusion

In conclusion, Ni(II) complexes with chiral tridentate ferrocenylphosphines are able to catalyze hydroamination reactions of electron-poor olefins. High activities and moderate to excellent

enantioselectivities were found in the case of the reaction of aliphatic and aromatic amines with methacrylonitrile. The reaction efficiency, and particularly the enantioselectivity, tolerates only very minor alterations to the substrates and still lacks generality.

Notwithstanding the substrate-limitation of this Ni(II)-catalyst, a possible use in hydrothiolation or classical asymmetric Michael addition could provide interesting results.

Works are currently in progress in order to develop a catalytic system for the addition of aliphatic and aromatic amines to prochiral non-activated olefins.

4. Experimental

4.1. General

All reactions with air- or moisture-sensitive materials were carried out under Argon using standard Schlenk techniques or in a glove box under nitrogen. The routine $^{31}P\{^1H\}$, $^{13}C\{^1H\}$, and ^1H NMR spectra were measured in the given solvent on either a *Bruker Avance* 200 [frequency in MHz: ^{13}C: 50.32, ^1H: 200.13] or *Bruker Avance* 250 [frequency in MHz: ^{31}P: 101.26, ^{13}C: 62.90, ^1H: 250.13] or *Bruker Avance* 300 [frequency in MHz: ^{31}P: 121.49, ^{19}F: 282.40, ^{13}C: 75.47, ^1H: 300.13] or *Bruker Avance DPX*500 [frequency in MHz: ^{31}P: 102.46, ^{13}C: 125.75, ^1H: 500.23] at room temperature. The chemical shifts δ are given in ppm relative to TMS, and referenced to the solvent signal for ^1H and $^{13}C\{^1H\}$ NMR, relative to an external reference for $^{19}F\{^1H\}$ [$CFCl_3$: δ 0.0 ppm] and $^{31}P\{^1H\}$ NMR [H_3PO_4 (85%):™ = 0.0 ppm]. The coupling constants J are given in hertz. The signals of MS-Measurements (EI-MS, FAB-MS, MALDI-MS) are given as m/z and the intensity in% of the base peak. IR-measurements were performed on a *Perkin–Elmer-Paragon* 1000-FT-IR-Spectrometer (measured in KBr, in Nujol or in $CHCl_3$): only the characteristic peaks are given in cm^{-1}. HPLC-Analysis *Agilent Series* 1100 or *HP* 1050 with a UV-detector (DAD); flow in mL/min, eluent (hexane/^{i}PrOH-ratio) and wavelengths are given in each experiment; column: *Chiralcel OD-H* (4.6 × 250 mm, particle 5 μm). GC analysis: *Fisons Instruments GC* 8000 *Series* or *ThermoQuest Trace GC* 2000 *Series* with FID-detector; columns: α-dex 120 (30 m × 0.25 mm × 0.25 μm), β-dex 120 (30 m × 0.25 mm × 0.25 μm) or γ-dex 120 (30 m × 0.25 mm × 0.25 μm). GC–MS analysis *Themo Finnigan TraceMS*, EI-MS, column: *Zebron* ZB-5 (30 m × 0.25 mm × 0.25 μm). Polarimeter measurements were performed on *Perkin–Elmer 341*; cell 10 cm, solution in $CHCl_3$ or in EtOH, 22 °C; c in g/100 mL. X-ray structural measurements were carried out by Dr. Isabelle Haller on a Siemens CCD diffractometer (Siemens SMART PLATFORM, with CCD detector, graphite monochromator, Mo-K_α-radiation). For the compounds **2–3**, CCDC 687280 (Compound **2b** in manuscript), CCDC 687281 (Compound **2a** in manuscript), and CCDC 687282 (Compound **3** in manuscript) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*R*)-[1-(Dimethylamino)ethyl]ferrocene was provided by SOLVIAS AG and was recrystallized as a tartrate salt according to a previously reported procedure.[25] The substrates needed for the hydroamination catalysis were distilled under Argon in the presence of (3–4 Å) molecular sieves. The full characterization of the chiral catalysis products has been reported previously.[16]

4.1.1. (*S*)-2-Diphenylphosphino-1-[(1*R*)-1-(dimethylamino)-ethyl]ferrocene ((*R*,*S*)-PPFA)

A solution of ^{t}BuLi (16 mL, 27.2 mmol, 1.65 M in pentane) was added at −78 °C to a solution of (*R*)-[1-(dimethylamino)ethyl]ferrocene (7 g, 27.2 mmol) in 30 mL Et_2O. After stirring for 30 min, the solution was allowed to warm to room temperature and stirred for 45 min. The mixture was then cooled to −78 °C, and $ClPPh_2$ (4.5 mL, 24.5 mmol) dissolved in 10 mL Et_2O was added dropwise. After warming to room temperature overnight, a saturated aqueous solution of $NaHCO_3$ was added to the solution and the product was extracted with Et_2O, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent yielded the crude solid product that was purified by recrystallization (EtOH/EtOAc or EtOH/hexane) and by flash chromatography (hexane/EtOAc = 5:1 + 5% NEt_3): 9.1 g (84.2%). ^1H NMR (250.13 MHz, CD_2Cl_2): δ 1.26 (d, 3H, J = 6.7, CH*Me*), 1.81 (s, 6H, N*Me*$_2$), 3.89 (m, 1H, CH(cp)), 3.95 (s, 5H, CH(cp′)), 4.21 (q, 1H, J = 6.7, C*H*Me), 4.28 (m, 1H, C*H*(cp)), 4.42 (s, 1H, C*H*(cp)), 7.20 (m, 5H, C*H*(Ph)), 7.39 (m, 3H, C*H*(Ph)), 7.63 (m, 2H, C*H*(Ph)). $^{13}C\{^1H\}$ NMR (75.47 MHz, $CDCl_3$): δ 8.1 (CH_3, CH*Me*), 38.7 (N*Me*$_2$), 57.1 (*C*HMe), 68.2 (CH(cp)), 69.3 (CH(cp)), 69.6 (CH(cp′)), 71.6 (CH(cp)), 79.78 (C(cp)), 97.3 (C(cp)), 126.8, 127.2, 127.8, 128.6, 132.1, 135.2 (*C*H(Ph)), 139.3, 141.6 (*C*(Ph)). $^{31}P\{^1H\}$ NMR (101.25 MHz, CD_2Cl_2): δ −22.14 (*P*Ph$_2$). EA: Anal. Calcd for $C_{26}H_{28}FePN$ (441.33): C, 70.76; H, 6.39; N, 3.17; P, 7.02. Found: C, 70.88; H, 6.38; N, 3.14; P, 7.10.

4.1.2. Bis{(1*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl}-cyclohexylphosphine, ((*R*,*S*)-Pigiphos)

At first, (*R*,*S*)-PPFA (7 g, 15.9 mmol) was dissolved at 40 °C in degassed CH_3COOH (30 mL) containing TFA (1.2 mL, 15.9 mmol). Next, H_2PCy (1.05 mL, 7.9 mmol) was added and the mixture was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure (60 °C, HV) and EtOAc was added. The resulting precipitate was filtered and washed with hexane/EtOAc = 1:1, yielding the pure product. The solvent of the mother liquor was also removed under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc = 3:1) and recrystallized from hexane at −20 °C: 6.101 g (85.2%), orange microcrystals. ^1H NMR (250.13 MHz, CD_2Cl_2): δ 0.7–1.7 (m, 11H, *Cy*), 1.59 (dd, 3H, J = 6.5, CHC*H*$_3$), 1.65 (dd, 3H, J = 7.5, CHC*H*$_3$), 2.90 (m, 1H, C*H*CH$_3$), 3.15 (m, 1H, C*H*CH$_3$), 3.80 (s, 5H, C*H*(cp′)), 3.84 (s, 5H, C*H*(cp′)), 3.90 (s, 1H, C*H*(cp)), 4.01 (m, 2H, C*H*(cp)), 4.09 (m, 1H, C*H*(cp)), 4.26 (m, 2H, C*H*(cp)), 7.20 (d, 5H, J = 3.5, C*H*(Ph)), 7.26 (m, 5H, C*H*(Ph)), 7.39 (m, 6H, C*H*(Ph)), 7.64 (m, 4H, C*H*(Ph)). $^{31}P\{^1H\}$ NMR (101.26 MHz, $CDCl_3$): δ −25.15 (d, J = 11.8, P_APh$_2$), −25.07 (d, J = 28.9, P_BPh$_2$), 18.04 (dd, J = 11.1, J = 29.7, *P*Cy). EA: Anal. Calcd for $C_{54}H_{55}Fe_2P_3$ (908.64): C, 71.38; H, 6.10; P, 10.23. Found: C, 71.42; H, 6.30; P, 10.26.

4.1.3. [NiCl((*R*,*S*)-Pigiphos)]PF_6, 1a

At first, $NiCl_2{\cdot}6H_2O$ (52 mg, 0.22 mmol) was dissolved in EtOH (2 mL) and the resulting green solution was poured into an orange toluene solution (5 mL) of (*R*,*S*)-*Pigiphos* (200 mg, 0.22 mmol). Upon addition of $TlPF_6$ (84.5 mg, 0.24 mmol), the solution turned red. The mixture was stirred at room temperature for 1 h. TlCl was removed by filtration, and the volatiles were removed under reduced pressure, and the product was recrystallized from CH_2Cl_2/hexane: 224.5 mg (90.5%) of red crystals. ^1H NMR (300.13 MHz, CD_2Cl_2): δ 0.8–2.7 (m, 11H, C*H*$_2$(Cy) or C*H*(Cy)), 1.90 (m, 6H, 2 × CHC*H*$_3$), 3.44 (m, 2H, 2 × C*H*Me), 3.72 (s, 5H, 5 × C*H*(cp)), 3.84 (s, 5H, 5 × C*H*(cp)), 4.42 (m, 2H, 2 × C*H*(cp)), 4.61 (m, 1H, C*H*(cp)), 4.65 (m, 1H, C*H*(cp)), 4.78 (m, 1H, C*H*(cp)), 4.84 (m, 1H, C*H*(cp)), 7.1–7.8 (m, 18H, 18 × C*H*(Ph)), 8.05 (m, 2H, C*H*(Ph)). $^{31}P\{^1H\}$ NMR (121.49 MHz, CD_2Cl_2): δ −143.78 (heptet, J_{PF} = 710.35, *P*F$_6$), 9.9 (d br, J_{cis} = 75.1, 2 × *P*Ph$_2$), 73.87 (dd, J = 60.1, J = 70.1, *P*Cy). $^{13}C\{^1H\}$ NMR (75.47 MHz, $CDCl_3$): δ 14.5, 14.6 (2 × *C*H$_3$CH), 24.9, 25.2, 26.2, 28.4, 29.4, 31.4 (*C*H$_2$(Cy) or *C*H(Cy)), 37.6, 37.9 (PCHCH$_3$), 69.3, 69.4, 70.1, 70.5 (*C*H(cp)), 70.8 (2 × *C*H(cp′)), 73.5, 74.5 (*C*H(cp)), 88.5 (2 × P*C*(cp)), 127.7–135.0 (20 × *C*H(Ph) + 4 × *C*(Ph)). MS (HiResMALDI): m/z 1001 (80, $[M]^+$),

965 (8, $[M–Cl]^+$, 845 (100, $[M–Cl–Fecp]^+$; Monoisotopic mass, calc: 1001.1252; found: 1001.1254. EA: Anal. Calcd for $C_{54}H_{55}F_6P_4ClFe_2Ni + CH_2Cl_2$ (1147.75): C, 55.74; H, 4.78. Found: C, 55.71; H, 5.09.

4.1.4. [Ni((*R*,*S*)-Pigiphos)(THF)](ClO$_4$)$_2$ 1b

$Ni(ClO_4)_2·6H_2O$ (183 mg, 0.5 mmol) and (*R*,*S*)-Pigiphos (398 mg, 0.44 mg) were dissolved in THF (10 mL). The mixture was stirred for 1 h at room temperature yielding a dark red solution. The solvent was removed under reduced pressure (HV), and the solid was washed twice with hexane (in a glove box). The product was dissolved in THF (20 mL) and purified by filtration of the suspension. Evaporation of the solvent yielded 454 mg (84.7%) of a dark red hydroscopic solid. ^{1}H NMR (300.13 MHz, THF-d_8): δ 0.8–2.7 (m, 11H, CH_2(Cy) or C*H*(Cy)), 1.89 (m, 4H, CH_2), 2.27 (m, 6H, 2 × CHCH_3), 2.71, 2.76 (m, 2H, 2 × C*H*Me), 3.72 (m, 4H, OCH_2), 3.80 (s, 5H, 5 × *CH*(cp)), 4.16 (s, 1H, C*H*(cp)), 4.37 (s, 5H, 5 × *CH*(cp)), 4.79 (m, 1H, C*H*(cp)), 4.85 (m, 1H, C*H*(cp)), 4.92 (m, 1H, C*H*(cp)), 5.21 (m, 1H, C*H*(cp)), 5.47 (m, 1H, C*H*(cp)), 6.72 (m, 2H, C*H*(Ph)), 7.17 (m, 2H, C*H*(Ph)), 7.43 (m, 4H, C*H*(Ph)), 7.62 (m, 4H, C*H*(Ph)), 7.73 (m, 4H, C*H*(Ph)), 8.10 (m, 2H, C*H*(Ph)). ^{31}P{^{1}H} NMR (121.49 MHz, THF-d_8): δ 6.31 (dd, J = 84.7, J = 247.8, P_APh2), 10.39 (dd, J = 65.7, J = 247.5, P_BPh2), 74.26 (dd, J = 83.9, J = 67.5, *P*Cy). ^{13}C{DEPT} NMR (75.47 MHz, THF-d_8): δ 12.36 (*C*H_3CH), 22.8 (*C*H(Cy)), 25.3 (*C*H_2), 25.8, 29.3, 31.0 (*C*H_2(Cy)), 36.4 (P*C*HCH$_3$), 65.1, 65.2 (*C*H(cp)), 66.1 (O*C*H_2), 68.9, 69.8 (2 × *C*H(cp′)), 69.5, 72.0 (*C*H(cp)), 126.0–134.0 (20 × *C*H(Ph)).

4.1.5. [Ni((*R*,*S*)-Pigiphos)(NCCH$_3$)](ClO$_4$)$_2$ 1c

At first, $Ni(ClO_4)_2·6H_2O$ (120.7 mg, 0.33 mmol) and (*R*,*S*)-Pigiphos (300 mg, 0.33 mmol) were dissolved in CH_3CN/Et_2O (20 mL, 1:1). The mixture was stirred for 1 h at room temperature. The resulting red-violet solution was filtered through a 0.45 μm Millipore, the solvent removed under reduced pressure (HV), and the solid washed with hexane. After drying: 304 mg (76.3%) of a red powder. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.5–2.8 (m, 11H, CH_2(Cy) or C*H*(Cy)), 1.91 (m, 6H, 2 × CHCH_3), 1.99 (s, CH_3CN), 3.42 (m, 1H, C*H*Me), 3.75 (m, 1H, C*H*Me), 3.90 (s, 5H, 5 × *CH*(cp)), 4.19 (s, 5 H, 5 × *CH*(cp)), 4.35 (s, 1H, C*H*(cp)), 4.72 (s, 1H, C*H*(cp)), 4.77 (s, 1H, C*H*(cp)), 4.86 (s, 1H, C*H*(cp)), 5.01 (s, 1H, C*H*(cp)), 5.08 (m, 1H, C*H*(cp)), 6.92 (m, 2H, C*H*(Ph)), 7.44 (m, 2H, C*H*(Ph)), 7.5–7.9 (m, 12H, C*H*(Ph)), 8.0 (m, 4H, C*H*(Ph)). ^{31}P{^{1}H} NMR (121.49 MHz, $CDCl_3$): δ 9.6 (dd, J = 69.1, J = 188.8, P_APh2), 18.6 (dd, J = 65, J = 189, P_BPh2), 84.75 (d br, J = 64, *P*Cy). ^{13}C{DEPT} NMR (75.47 MHz, $CDCl_3$): δ 14.26 (*C*H_3CH), 14.36 (*C*H_3CH), 24.0–28.0 (*C*H_2(Cy)), 38.1, 38.2 (P*C*HCH$_3$), 70.6 (*C*H(cp)), 71.3, 71.7 (2 × *C*H(cp′)), 72.3, 72.6, 73.0, 74.9, 76.1 (*C*H(cp)), 129.5, 129.6, 131.9, 132.4, 132.9, 133.2, 133.5, 133.7, 134.9, 135.3 (20 × *C*H(Ph)). IR (KBr): 2856.7 (br, CH), 2293.0, 2261.5 (s, CN), 1460.9 (s), 1377.0 (s), 1088.2 (s), 973.5 (s).

4.2. General hydroamination procedure

In the glove box or in a Teflon valve flask (Young), 0.02–0.1 mmol (5 mol %) of $Ni(ClO_4)_2·6H_2O$ and 0.02–0.1 mmol (5 mol %) of the ligand (*R*,*S*)-Pigiphos were dissolved in THF (3 mL). The resulting red-purple solution was stirred at room temperature for 20 min, and then 0.4–2.0 mmol of olefin was added. The solution was stirred for an additional 30 min. In some cases, precipitation of the $[Ni(PPP)(Olefin)]^{2+}$ was observed. After the addition of 0.2–1.0 mmol of the amine, the solution was stirred overnight at room temperature. After 24 h, hexane was added to precipitate the catalyst, and the product was purified by flash column chromatography. The isolated product was characterized by ^{1}H and ^{13}C NMR, EA, and GC–MS.

4.2.1. (+)-[2-(*R*)-Methyl-3-(morpholinium)propanenitrile][(*S*)-1,1′-binaphthyl-2,2′-diylphosphate], 2a

A solution of (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (80.4 mg, 0.231 mmol) and 2-methyl-3-(morpholin-4-yl)propanenitrile (37 mg, 0.231 mmol, 64% ee from the catalysis) in MeOH (1 mL) was stirred at room temperature for 15 min (all the products were dissolved). Et_2O was added, and a white solid precipitated. The suspension was cooled at −20 °C and was stirred for 4 h. The solid was filtered off and washed with Et_2O (3 × 20 mL). After drying (HV): 95 mg (80.9% yield). X-ray-quality crystals were obtained by recrystallization from EtOH/Et_2O. ^{1}H NMR (250.13 MHz, D_2O): δ 0.79 (d br, 3H, CH*Me*), 2.62 (m br, 7H, CH_2CH + C*H*Me + (CH_2)$_2$N), 3.36 (s br, 4H, (CH_2)$_2$O), 5.82 (s br, 2H, arom.), 6.28 (s br, 2H, arom.), 6.49 (s br, 2H, arom.), 7.15 (s br, 2H, arom.), 7.35 (s br, 2H, arom.), 7.61 (s br, 2H, arom.). ^{31}P{^{1}H} NMR (101.25 MHz, $CDCl_3$): δ 6.54 (PO_4^-). $[\alpha]_D$ = +335.2 (*c* 1, CH_2Cl_2) rot. = +0.889°. MS (ESI+Q1MS): *m*/*z* 155.3 (40, $[M]^+$), 87.3 (10, $[M–CH_2CH(CH_3)CN]^+$. EA: Anal. Calcd for $C_{28}H_{27}N_2O_5P$ (52.51): C, 66.93; H, 5.42; N, 5.57. Found: C, 66.74; H, 5.44; N, 5.45.

4.2.2. (−)-[2-(*R*)-Methyl-3-(morpholinium)propanenitrile][(*R*)-1,1′-binaphthyl-2,2′-diylphosphate], 2b

A solution of (*R*)-(−)-1,1′–binaphthyl-2,2′-diyl hydrogen phosphate (67.4 mg, 0.19 mmol) and 2-methyl-3-(morpholin-4-yl)propanenitrile (31 mg, 0.19 mmol, 64% ee from the catalysis) in MeOH (2 mL) was stirred at room temperature for 1 h (all the products were dissolved). Next, Et_2O was added and a small amount of a white solid precipitated. The suspension was cooled to −20 °C for 4 h, and then the white solid was filtered off and washed with Et_2O (3 × 20 mL). After drying (HV): 14 mg (14.6% yield). X-ray quality crystals were obtained by recrystallization from EtOH/Et_2O. ^{1}H NMR (250.13 MHz, CD_2Cl_2): δ 1.35 (d, 3H, CH*Me*), 2.99 (m br, 6H, CH_2CH + (CH_2)$_2$N), 3.40 (m br, 1H, C*H*CH$_3$), 3.79 (s br, 4H, (CH_2)$_2$O), 7.33–7.53 (m, 8H, arom.), 7.98 (m, 4H, arom.). ^{31}P{^{1}H} NMR (101.25 MHz, $CDCl_3$): δ 5.27 (PO_4^-). $[\alpha]_D$ = -337.3 (*c* 1, CH_2Cl_2) rot. −0.657°. EA: Anal. Calcd for $C_{28}H_{27}N_2O_5P$ (502.51): C, 66.93; H, 5.42; N, 5.57. Found: C, 66.87; H, 5.58; N, 5.33.

The salt (14 mg, 0.026 mmol) was hydrolyzed with 0.1 M NaOH. The mixture was stirred at room temperature for 1 h. Extraction with Et_2O (3 × 10 mL) yielded 4 mg (97%) of the pure (*R*)-enantiomer of 2-methyl-3-(morpholin-4-yl)propanenitrile (product confirmed by GC–MS and ^{1}H NMR); retention time in GC4 (β-dex, 92 °C iso): 139.2 min (major product).

4.2.3. (−)-[3-(*R*)-(Phenylammonium)butanenitrile][(*R*)-1,1′-binaphthyl-2,2′-diylphosphate], 3

A solution of (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (63.04 mg, 0.181 mmol) and 3-(phenylamino)butanenitrile (29 mg, 0.181 mmol, 18% ee from the catalysis) in MeOH (1 mL) was stirred at room temperature for 15 min (all the products were dissolved). Et_2O was added, and a white solid precipitated. The suspension was cooled to −20 °C for 24 h, and the white solid was filtered off and washed with Et_2O (3 × 20 mL). After drying (HV): 46 mg (50% yield; expected from 18% ee: 59%). Crystals suitable for X-ray diffraction were obtained after recrystallization with EtOH/Et_2O. ^{1}H NMR (250.13 MHz, D_2O): δ 1.47 (d, 3H, J = 7, CH*Me*), 2.74 (dd, 1H, J = 8, J = 16, C*H*H′), 2.90 (dd, 1H, J = 4, J = 16, CH*H*′), 3.71 (m br, 1H, C*H*CH$_3$), 4.5 (s br, 1H, N*H*), 7.2–7.6 (m, 8H, arom.), 7.98 (m, 4H, arom.). ^{31}P{^{1}H} NMR (121.49 MHz, $CDCl_3$): δ 4.53 (PO_4^-). $[\alpha]_D$ = −204.2 (*c* 1, CH_2Cl_2) rot. −0.326°.

The salt (24 mg, 0.047 mmol) was hydrolyzed with 0.1 M NaOH. Extraction with Et_2O (3 × 10 mL) yielded 8 mg (95%) of the pure (*R*)-enantiomer of 3-(phenylamino)butanenitrile (product con-

firmed by GC–MS and ^{1}H NMR); retention time in HPLC (OD-H, 98:2 hexane/^{i}PrOH, 1 mL/min, DAD 254 nm): 52.6 min (major product).

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