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New 5,5′-disubstituted BINAP derivatives: Syntheses and pressure and electronic effects in Rh asymmetric hydrogenation

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Abstract

A library of 5,5′-disubstituted BINAP derivatives were synthesized in good yield from optically pure BINAP and evaluated for the Rh-catalyzed homogeneous asymmetric hydrogenation of (α)-acylaminoacrylate ester, with ee of up to 77% being obtained with the phenyl derivative. The enantiomeric excess variation was followed according to the groups introduced in the 5,5′-position of BINAP and for a range of pressure from 5 to 30 bar.

Keywords: Asymmetric catalysis; Rhodium; Hydrogenation; Ligand effect

Chiral diphosphines have been known for more than 30 years [1,2], to be the most efficient type of ligands for the asymmetric hydrogenation of C=C and C=O bonds, one of the most important application of enantioselective catalysis [3]. The first developments by Knowles and Sabacky [4], Horner et al. [5], and Kagan and coworkers [6] were rapidly followed by the first successful commercial application of the Rh-catalyzed hydrogenation of prochiral enamides in the Monsanto L-DOPA process [7] and the preparation of pharmaceuticals, agrochemicals, fragrances, and flavours [8]. In 1980, Noyori and coworkers published the synthesis of BINAP [9,10] (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), which has further open the field of application of asymmetric hydrogenation. Since then, the mechanism of the reaction [11] has been elucidated, thousands of chiral ligands and their transition-metal complexes have been reported [12]. Many of them, closely related to the BINAP itself, are highly effective in the asymmetric formation of C–H, C–C, C–O, and C–N bonds and for transition-metal-catalyzed asymmetric synthesis in general [13–15].

The research undertaken to date in asymmetric hydrogenation relates almost exclusively to the development of new chiral inductors to improve the selectivity of the reactions. The key/hole concept generally used to adapt the chiral catalyst to the prochiral substrate is however, often not operating properly. On the contrary, many examples demonstrate the importance of the operating conditions, such as the hydrogen pressure, on the ee during enantioselective catalytic hydrogenations [16a]. Kinetic factors rather than thermodynamic account for such observations, as demonstrated from the determination of the reaction mechanism [17]. This study pointed that a small and achiral molecule like hydrogen, can indeed exert a very strong influence on measured ee. With regard to the asymmetrical reductions of "enamide" type substrates by molecular hydrogen, it is noteworthy that most of hydrogen pressure effects lead to a *decrease* of the enantioselectivity. The situation is even more complex since it is the dissolved hydrogen concentration and not the pressure which is responsible for ee variations. The reactor, being in charge of gas–liquid mixing, is also involved somehow [16,18]. The situation is complex but rather clear: the pathway to further understand the structure/enantioselectivity relationship, that would ultimately leads to more general predictive tools, must go through the decoupling of possible pressure and conversion effects on ee while proceeding with a systematic approach of intrinsic (molecular) effects. Obviously, because many tests are being performed, such an approach

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needs specific tools able to handle small quantities of expensive chiral inductors (BINAP ≈ 80,000 € kg^{-1}) [16] within a broad range of operating conditions [19,20].

In order to extend the scope of our first studies, a library of 5,5′-disubstituted BINAP derivatives have been synthesised and a significant number of catalytic systems of the type Rh/BINAP-derivatives (seven catalytic systems) with various electronic and steric properties, all featuring the same ligand backbone, have been screened for the asymmetric hydrogenations of three prochiral(acylamino)acrylic esters within a range of pressure from 5 to 30 bar.

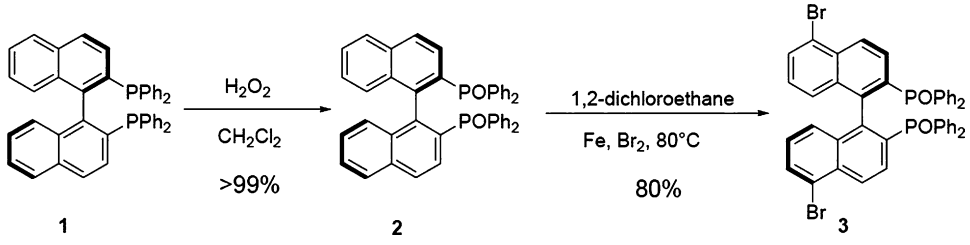
1. Results and discussion

1.1. Synthesis

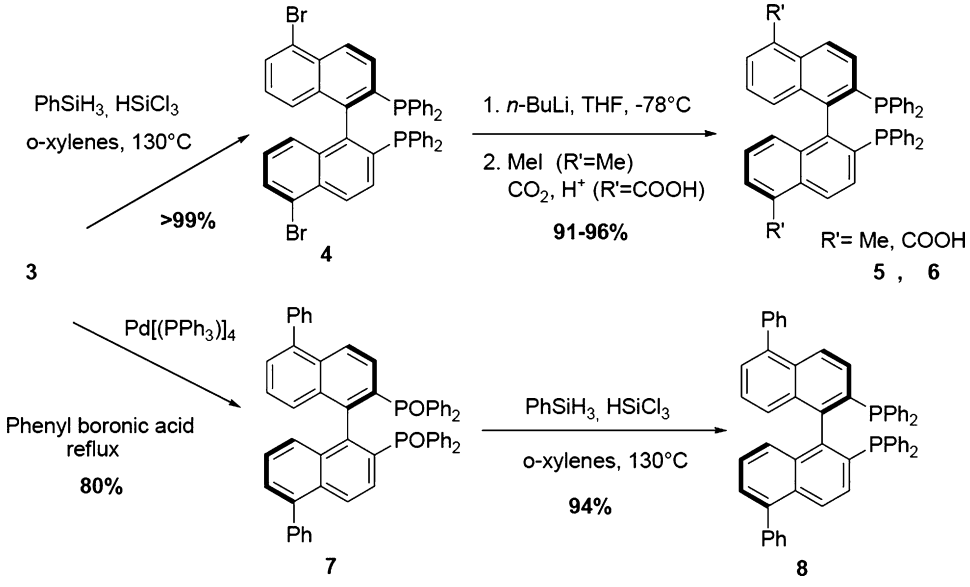
Most of the BINAP derivatives were usually prepared from BINOL or protected BINOL with a phosphination reaction at the end of the synthesis [21]. Lemaire and coworkers [22] described a new strategy to obtain BINAP derivatives directly from BINAP itself. Firstly, optically pure (*R*)-BINAP was transformed (Scheme 1) into its corresponding dioxide **2** followed by a regioselective bromination. The 4,4′-positions were brominated in the presence of pyridine [23] according to Kockritz and coworkers while the 5,5′-positions were brominated in the presence of iron as catalyst. In both cases, brominations were regioselective, with only a trace of monobrominated by-products. The dibrominated phosphines were both obtained in 80% isolated yield [24]. In the literature, the only way to functionalize the 5,5′-position is nitration [25] or sulfonation [26]. Our method required a strong Lewis acid. Phosphine oxides are Lewis bases [27] and are complexed during electronic substitution in presence of Lewis acid. Although the 4,4′-positions, close to the phosphine oxide, were the most reactive, the presence of a Lewis acid deactivate this position by complexing the phosphine oxide; Br_2 (activated by the presence of Fe) would brominate the less deactivated 5,5′-position. To our knowledge, this method is the first report, which leads to a dibrominated BINAP at the 5,5′-positions [28]. In order to study electronic effect in the Rh-catalyzed homogeneous asymmetric hydrogenation of (α)-acylaminoacrylate ester we were interested in the synthesis of new 5,5′-disubstituted BINAP derivatives by this method.

Our synthesis began from readily available BINAP (**1**), which was treated with H_2O_2 in dichloromethane to give BINAPO (**2**) and the treatment of (**2**) with bromine and iron at 80 °C in 1,2-dichloroethane give 5,5′-dibromoBINAPO (**3**) (Scheme 1).

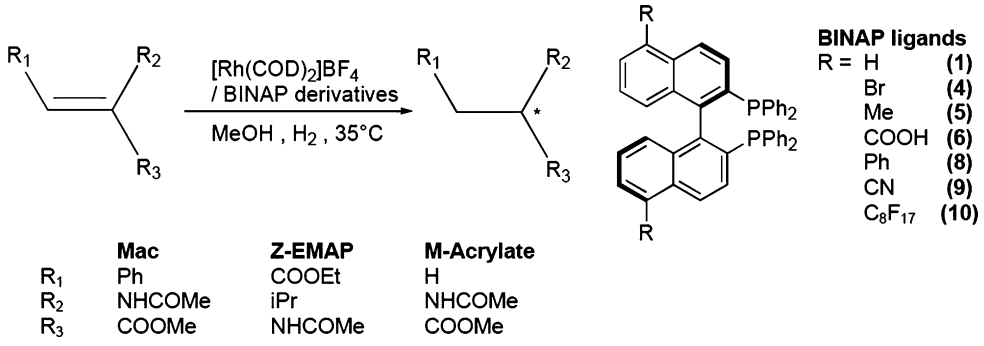
The 5,5′-disubstituted BINAP derivatives were synthesized starting from (**3**) by two different approaches (Scheme 2). Firstly, compound (**4**) was synthesized from (**3**) in excellent yields by reduction with a mixture of $PhSiH_3$ and $HSiCl_3$ at 130 °C. Then, compounds (**5**) and (**6**) were obtained in very good yield (91–96%) by lithiation of (**4**) with *n*-butyl lithium followed by



Scheme 1. Synthesis of 5,5′-dibromoBINAPO.



Scheme 2. Synthesis of 5,5′-(diphenyl, dimethyl, diacides)BINAP.



Scheme 3. Asymmetric hydrogenation of pro-chiral acyl(amino)acrylic ester with (*R*)-5,5′-substitued BINAP derivatives.

treatment with the desired electrophile. In the second approach, (**8**) was synthesized from (**3**) by halogen metathesis, Suzuki coupling, or Pd-catalyzed phosphination reaction followed by reduction with a mixture of $PhSiH_3$ and $HSiCl_3$ at 130 °C. All these new compounds were fully characterized.

1.2. Evaluation

The study of the test reaction with different ligands was performed in a stainless steel mini-autoclave of 15 mL. (Amtec; http://www.amtec-chemnitz.de). This autoclave is equipped with magnetic stirring (2200 rpm) and operates within a large range of hydrogen pressure (1–30 bar). An evaluation of the influence of the hydrogen pressure on the enantioselectivity was performed on the BINAP derivatives chiral ligands complexed with a rhodium precursor, $[Rh(COD)_2]BF_4$ and for three substrates (Scheme 3).

First, a study on the influence of the catalyst ageing on the activity was performed. After 6 days storage at 0 °C, stock solutions of catalyst (*R*)-5,5′-diperfluoroBINAP (**10**) and (*R*)-5,5′-diacidesBINAP (**6**) display a decrease of activity of more the 50% (Fig. 1). In order to avoid any interference with deactivation, it was decided to only use freshly prepared solution (1 day) for all catalysts.

A recent work has demonstrated that in most cases (65%), an increase in the hydrogen concentration leads to smaller enantioselectivities and higher catalytic activities [16]. For production, catalysts for which both the activity and enantioselectivity are promoted with hydrogen concentration (pressure) would be highly desirable. However, prediction tools in asymmetric catalysis are scarce and, so far, not able to anticipate such effects.

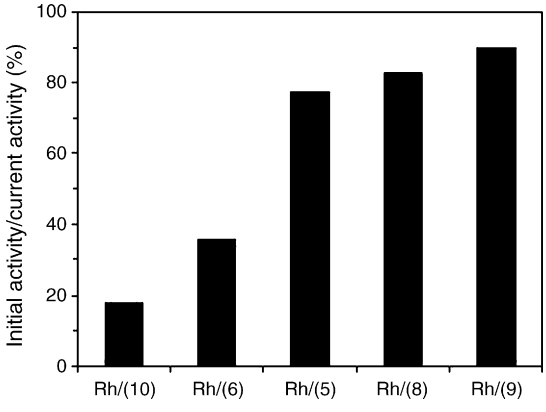


Fig. 1. Activity of catalytic systems after 6 days computed in percent from initial activity.

In this work, up to 21 substrates/ligands systems have been investigated (Table 1). The observed variations of enantiomeric excess with the hydrogen pressure is not as marked as in previous studies [16], only one reaction system leading to a large ee variation from 6 to 50% ee (entry 21).

The substrates MAC and M-Acrylate display many similar behaviors (entries 1–14). Complete conversion (>96%) was obtained for all experiments. The enantiomeric excess was also constant with conversion. These closely related substrates only differ with the presence of a phenyl group on the (α)-acylaminoacrylic ester. That can lead to weak π–π stacking

Table 1
Influence of the hydrogen pressure on the enantiomeric excess

Entry	Substrate	Ligand	ee (%) at *P* (bar)		Configuration	EeEF[a]
			5	30		
1	MAC	1	14	14	*S*	0
2		5	21	21	*S*	0
3		4	31	31	*S*	0
4		8	34	34	*S*	0
5		6	27	27	*S*	0
6		10	26	31	*S*	0.09
7		9	14	18	*R*	0.13
8	M-Acrylate	1	9	9	*S*	0
9		5	14	20	*S*	0.18
10		4	3	3	*S*	0
11		8	29	24	*S*	−0.09
12		6	24	24	*S*	0
13		10	24	24	*S*	0
14		9	9	20	*R*	0.38
15	*Z*-EMAP	1	66	57	*R*	−0.07
16		5	60	60	*R*	0
17		4	63	63	*R*	0
18		8	77	72	*R*	−0.03
19		6	70	60	*R*	−0.08
20		10	21	50	*R*	0.41
21		9	6	50	*S*	0.79

All reactions were carried out at 35 °C with [substrate] = 0.1 M and [catalyst] = (10^{-3} to 10^{-4} M) under hydrogen pressure (5–30 bar) in 4 mL of degassed MeOH. Yield are all >96% as checked by GC analysis.

[a] See text.

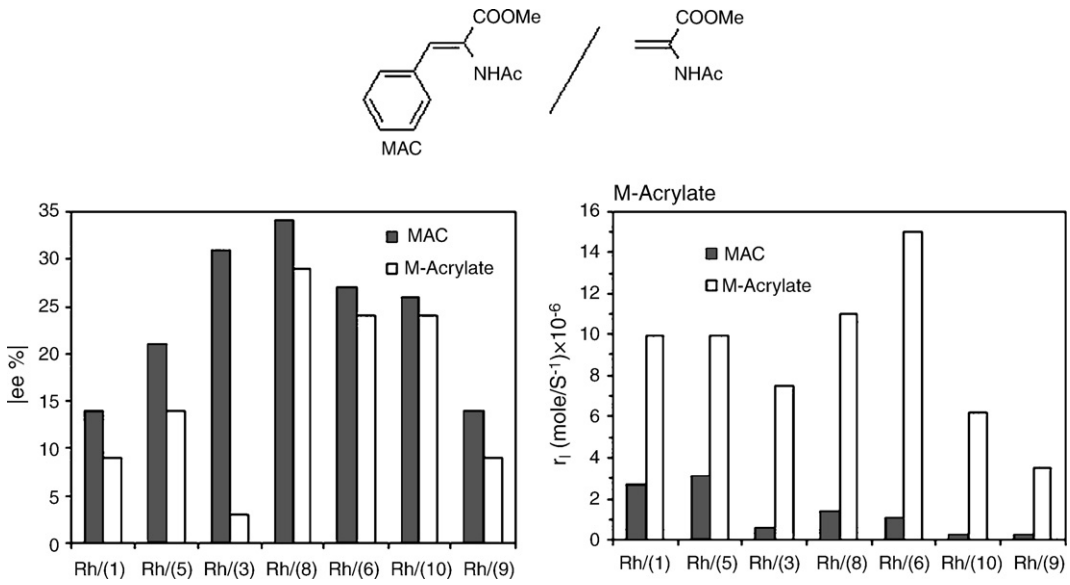


Fig. 2. Comparison between MAC/M-Acrylate, conditions: 5 bar, $T = 35^{\circ}C$, methanol.

interactions with one of the phenyl groups of the BINAP (**1**) derivatives. Such interaction may explain the better ee generally obtained for the MAC albeit with slower reaction rates (Fig. 2).

Considering the effect of pressure on the enantiomeric excess for the two substrates MAC and M-Acrylate, only a minor influence was observed under a large range of hydrogen pressure (5–30 bar) for most of the Rh-BINAP derivatives. Positive effect of hydrogen pressure on the ee was noticed only in the case of electro-withdrawing groups like (CN (**9**), C_8F_{17} (**10**)) [29,30] on the 5,5′-position. Interestingly, only in one instance, ligand (*R*)-5,5′-diphenylBINAP (**8**) and M-Acrylate, a decrease of ee with increasing hydrogen concentration was observed (entry 11). Thus, among the 14 reactions systems (entries 1–14), 9 are pressure insensitive (with respect to ee), 4 give positive effects and 1 gives a negative effect.

The hydrogenation of the ethyl 4-methyl-3-acetamido-2-pentanoate (*Z*-EMAP) [31] under the same conditions generally, leads to higher ee's, up to 77% (entry 18). Among the seven catalytic systems, the distribution of positive effect (entries 20, 21), negative effect (entries 15, 18, 19), and no effect (entries 15–21) of hydrogen concentration (pressure) is roughly the same.

In order to quantify the observed influence of the hydrogen pressure on enantiomeric excess, the following Enhancement Factor (eeEF = enantiomeric excess Enhancement Factor) is proposed:

$$\mathrm{eeEF_{Theory}} = \frac{\mathrm{ee}_{P_{H_2\to\infty}} - \mathrm{ee}_{P_{H_2\to 0}}}{\mathrm{ee}_{P_{H_2\to\infty}} + \mathrm{ee}_{P_{H_2\to 0}}},$$

$$\mathrm{eeEF_{Exp}} = \frac{\mathrm{ee}_{P_{H_2\max}} - \mathrm{ee}_{P_{H_2\min}}}{\mathrm{ee}_{P_{H_2\max}} + \mathrm{ee}_{P_{H_2\min}}}$$

where $\mathrm{ee}_{P_{H_2\to 0}}$ and $\mathrm{ee}_{P_{H_2\to\infty}}$ are the enantiomeric excess that would be obtained at very low hydrogen pressure and high hydrogen pressure, respectively. In practice, $\mathrm{eeEF_{exp}}$ is used in which $\mathrm{ee}_{P_{H_2\min}}$ and $\mathrm{ee}_{P_{H_2\max}}$ are the ee obtained under the limits of experimental pressure range for the study. This "enhancement" criteria, which varies between −1 and +1, is very useful since it accounts for both the amplitude and the beneficial (+ sign) or detrimental (− sign) effect of increasing pressure. Thus a quick look at eeEF provides many information on pressure effects or other influences on ee. However, it is not adapted for systems displaying configuration change (e.g. examples where the sign of ee changes with pressure).

Considering all the ligands and substrates, the pressure effect on ee is not very much marked. Out of the 21 reaction systems, 11 are not influenced by pressure (Table 1, eeEF = 0), 6 give positives effects (eeEF > 0) and 4 give negatives effects (Table 1, eeEF < 0), with a remarkable positive effect (+0.79) for entry 21 (6–50% ee). These results are very different from those found in the literature, specially for the substrate methyl *Z*-α-acétamidocinnamate (MAC), for which a marked preference for negative effect has been found (16 out of 19 cases) [16]. More generally, an extensive literature search on pressure effects on ee, including Ru and Rh and many different ligands [16], has resulted in a non-equivalent distribution of pressure effects: 53% with eeEF < 0, 15% with eeEF > 0 and 32% with eeEF = 0.

Albeit the quantitative comparison with literature results remains difficult since enantiomeric excess depend on many other parameters (solvent, temperature, reactor, etc.), it should be emphasized that the distribution of pressure effects (0% with eeEF < 0, 72% with eeEF > 0, 28% with eeEF = 0) observed in this study offers a striking contrast for which no explanation can be obtained yet.

Finally, it is noteworthy that all substrates display a common feature in relation with the effect of the electronic density at the phosphorus atoms on the activity and the enantioselectivity. Indeed according to the electron-withdrawing or electron-donating effect of the group introduced in the 5,5′-position of BINAP (**1**), the enantiomeric excess varies. For the acrylate substrate (Fig. 3), a regular variation of ee is observed with respect to the electon-withdrawing properties of the ligands

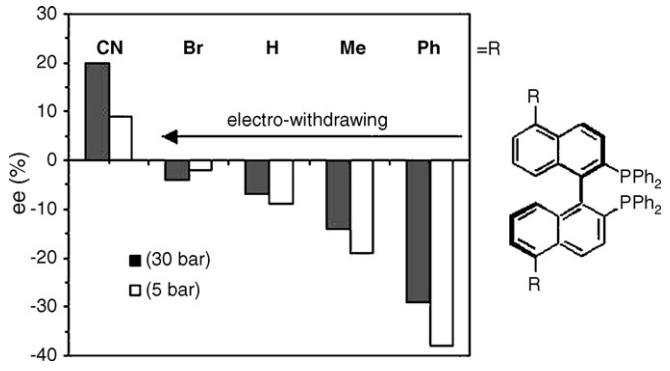


Fig. 3. Effect of the groups in the 5,5′-position of BINAP on the enantiomeric excess for M-Acrylate.

(Fig. 3). Attempts to find general correlations between the electronic properties of the ligands and ee have failed. This maybe due to the difficulty to choose the right parameter to describe the electronic property of the ligands. It is not possible to reduce the complexity of electronic properties of such ligands and their interaction with the metal centre to just one single parameter. Theoretical chemistry may help to explain electronic properties of the ligands.

In conclusion we have synthesized and tested various 5,5′-disubstituted BINAP derivatives (seven catalytic systems) for the Rh-catalyzed homogeneous asymmetric hydrogenation of (α)-acylaminoacrylate ester. We have shown that the BINAP derivatives generally lead to higher ee than BINAP (**1**) the best ligand being the 5,5′-diphenylBINAP (**8**). The nature of the alkyl groups in the 5,5′-position or in the *p*-phenyl position has a large influence on the variation of the enantiomeric excess with hydrogen pressure: either a steric hindrance, or an inductive electron-donating or electron-withdrawing effect allows to reverse the influence of the hydrogen pressure on the enantiomeric excess. More importantly, we have shown that the introduction of electron donating or electron withdrawing groups on the 5,5′-positions of the BINAP could have a direct influence on the enantiomeric excess and on the activity of catalyst (under identical operating conditions). Further work are devoted to the use of methods from theoretical chemistry to help understanding the results and built prediction tools.

2. Experimental

2.1. General methods

Solvents were dried with 4 Å molecular sieves and distilled under an argon on $LiAlH_4$ or purchased anhydrous (Aldrich or Acros). For catalytic tests, solvents were deoxygenated by repeated evacuation and argon purging. NMR spectra were recorded on Bruker AC 200 and DRX 300 apparatus. Chemical shifts are given in ppm using tetramethylsilane as the internal standard for ^1H and ^{13}C NMR spectra, and ^{31}P NMR from H_3PO_4. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. For the air-sensitive compounds, elemental analyses were not performed. Mass spectra were recorded on LCQ Advantage Thermofinnigan. Conversions and enantioselectivities (ee ± 1%) were determined by GC on a lipodex A (25 m × 0.25 mm) and CHIRASILVAL (25 m × 0.25 mm) column. All the yields are isolated yields. Hydrogenation experiments were performed in a mini-autoclave of stainless of 15 mL from Amtec (http://www.amtec-chemnitz.de).

The compound *Z*-EMAP (ethyl 4-methyl-3-acetamido-2-pentanoate) was prepared according to a published procedure [31]. The compound M-Acrylate (methyl 2-acetamidoacrylate) is commercially available (Aldrich).

2.2. (R)-BINAPoxide (2)

In a 250 mL round-bottomed flask were placed either (*R*)-BINAP (1) (3 g, 4.81 mmol) and 100 mL of CH_2Cl_2. The mixture was cooled to 0 °C and 10 mL of hydrogen peroxide H_2O_2 (35%) then added. The mixture was stirred for 4 h. Then 100 mL of water was added. Aqueous phases were extracted with 50 mL of CH_2Cl_2. The organics phases were washed with 50 mL of aqueous sodium hydrogen sulfite solution dried over Na_2SO_4 and evaporated to obtain a white solid (3.14 g, 4.8 mmol, quantitative yield). ^1H NMR (300 MHz, $CDCl_3$): 6.80 (d, 4H, $J = 3.7$), 7.2–7.3 (m, 8H), 7.3–7.5 (m, 12H), 7.6–7.7 (m, 4H), 7.8–7.9 (m, 4H). ^{31}P NMR (81 MHz, $CDCl_3$): 28.67. Mp: 256–258 °C $[\alpha]_D = +198.1$ (*c* 1, Benzene).

2.3. (R)-5,5′-DibromoBINAPO (3)

A solution of (*R*)-BINAPO (**2**) (4.8 g, 7.4 mmol) in 1,2 dichloroethane (45 mL) was added dropwise to a stirred refluxing solution of 1,2 dichloroethane, (65 mL), Br_2 (7.6 mL, 148 mmol, 20 eq.) and Fe (622 mg, 11.1 mmol, 1.5 eq.). After addition was completed, the mixture was heated at reflux overnight and then filtered to remove any solid iron. The organic layer was washed sequentially with H_2O, aqueous 1M sodium hydrogensulfite, saturated sodium hydrogen carbonate solution and brine. After drying over Na_2SO_4 the solvent was removed to obtain a white solid (4.85 g 6 mmol, 80.7%). ^1H NMR (200 MHz, $CDCl_3$): 6.62 (t, 2H, $J = 15.0$), 6.72 (d, 2H, $J = 9.0$), 7.2 7.5 (m, 20H), 7.55 (dd, 2H, $J = 3.0$, 1.0), 7.6–7.8 (m, 2H), 8.3 (dd, 2H, $J = 1.7$, 9.0). ^{13}C NMR (75 MHz, $CDCl_3$): 123.2, 126.5, 127.1, 127.3, 128.5, 128.7, 129.9, 131.6, 131.8, 132.1, 132.3, 132.5, 132.8, 132.9, 133.4, 135.0. ^{31}P NMR (81 MHz, $CDCl_3$): 29.20. $[\alpha]_D = +97.7$ ($c = 1$, DMF). ESI^+: $MH^+ = 813.32$. Mp: >300 °C. Calcd. C 65.05, H 3.72, P 7.62, Br 19.67; found C 65.34, H 4.05, P 7.46, Br 19.44.

2.4. (R)-5,5′-DibromoBINAP (4)

In a 250 mL round-bottomed flask under an inert atmosphere fitted with a reflux condenser was placed, (*R*)-5,5′-dibromoBINAPO (**3**) (3.9 g, 4.8 mmol), 65 mL of xylene and phenylsilane (28 mL, 219 mmol) was added. The mixture is stirred 10 min at room temperature after 10 min the trichlorosilane (22.13 mL, 219 mmol) was added dropwise, heated to

130 °C. After 15 h, the solution was cooled and stirred for 2 h, and NaOH (75 mL, 40%) was added very dropwise, the layer were separated and the aqueous phase washed with toluene; the organic layers were collected and washed with water, then HCl, and water. After drying over $MgSO_4$ the solvent was removed to obtain a white solid (3.68 g, >98%). ^{1}H NMR (300 MHz, $CDCl_3$): 6.58 (d, 10H, J = 4.3), 6.9–7.15 (m, 14H), 7.45–7.55 (m, 4H), 8.23 (d, 2H, J = 8.8). ^{13}C NMR (75 MHz, $CDCl_3$): 126.48, 127.57, 127.82, 128.54, 128.59, 128.64, 128.67, 128.72, 129.14, 130.9, 132.28, 133.14, 133.28, 133.41, 134.69, 134.83, 134.98. ^{31}P NMR (81 MHz, $CDCl_3$): 13.9. $[\alpha]_D$ = +78.1 (c = 1, DMF). HRLSIMS: MH^+. Calcd. 778.06, found 778.026. Mp: >300 °C. Calcd. C 67.71, H 3.87, Br 20.48, P 7.94; found C 67.1, H 4.0, Br 20.8, P 7.5.

2.5. (R)-5,5′-DiacidesBINAP (6)

A 50 mL three-necked round-bottomed flask under argon fitted with a low temperature thermometer, (*R*)-5,5′-dibromoBINAP (**4**) (500 mg, 0.641 mmol), THF (6.4 mL) was added at −78 °C. After stirred 10 min, a solution of *n*-BuLi (1.6 M in hexane, 0.8 mL, 1.282 mmol, 2 eq.) was added very dropwise and stirred 3 h at −78 °C. After 3 h the anion in suspension was then added via a canula to a Dewar containing an excess of crushed CO_2 in Et_2O (≈7 mL), this mixture gave a pink colour. The mixture was left overnight to allow slow degassing. 4 mL of HCl (0.5N) was then added to the mixture so that the colour becomes clear yellow. The solvents were then evaporated and the residue was dried to give a yellow powder (416 mg, 91% Rdt). ^{1}H NMR (300 MHz, DMSO): 6.86–7.03 (m, 10H), 7.43–7.46 (dd, 2H, J = 7, J = 1.0), 7.98 (dd, 2H), 8.9 (d, 2H), 13–13.5 (broad pic, 2 OH). ^{13}C NMR (75 MHz, DMSO): 125.07, 125.98, 128.2, 128.42, 128.76, 130.05, 130.65, 130.9, 131.53, 132.19, 132.39, 132.59, 132.88, 132.99, 133.23, 133.45, 133.65, 135.27, 135.44, 135.76, 135.91, 136.66, 136.91, 145.03, 168.64. ^{31}P NMR (81 MHz, DMSO): −15.7. $[\alpha]_D$ = +82.3 (c = 1, DMF). HRLSIMS: MH^+. Calcd. 710.17760, found 710.17766. Mp: >300 °C. Calcd. C 77.74, H 4.54, O 9, P 8.72; found C 75.96, H 5.098, O 10.75, P 8.178

2.6. (R)-5,5′-DiacidesBINAPO (6′)

In a 250 mL round-bottomed flask were placed either (*R*)-5,5′-diacidesBINAP (6) (3 g, 4.2 mmol) and 100 mL of CH_2Cl_2. The mixture was cooled to 0 °C and 10 mL of hydrogen peroxide H_2O_2 (35%) then added. The mixture was stirred for 4 h. Then 100 mL of water was added. Aqueous phases were extracted with 50 mL of CH_2Cl_2. The organic phases were washed with 50 mL of aqueous sodium hydrogen sulfite solution, dried over Na_2SO_4 evaporated to obtain a shining brown solid (3.14 g, 4.8 mmol, quantitative yield). ^{1}H NMR (300 MHz, DMSO): 6.4–6.85 (m, 20H), 7.3–7.6 (m, 6H), 7.65 (d, 2H), 8.9 (d, 2H, J = 9.025), 13–13.5 (broad pic, 2 OH). ^{13}C NMR (75 MHz, DMSO): 125.77, 127.24, 127.99, 128.13, 130.63, 131.4, 131.58, 131.81, 132.02, 133.49, 168.45. ^{31}P NMR (81 MHz, DMSO): 28.4. $[\alpha]_D$ = −30 (c = 1, DMF). HRLSIMS: MH^+. Calcd. 742.17, found 742.2. Mp: >300 °C. Calcd. C 74.4, H 4.3, O 12.9, P 8.3; found C 74.9, H 4.6, O 12.5, P 8.1.

2.7. (R)-5,5′-DimethylBINAP (5)

A 50 mL three-necked round-bottomed flask under argon fitted with a low temperature thermometer, (*R*)-5,5′-dibromoBINAP (**4**) (1.5 g, 1.923 mmol), THF (48 mL) was added at −78 °C using dry liquid nitrogen/acetone. After stirring at this temperature for 10 min, a solution of *n*-BuLi (1.6 M in hexane, 2.4 mL, 3.846 mmol, 2 eq.) was slowly added via syringe and it was stirred at this temperature for 3 h. And then MeI (0.239 mL, 3.846 mmol, 2 eq.) was added. The reaction mixture was stirred at this temperature for 1 h and then warmed to room temperature and stirred overnight. After removal of solvent, and LC separation on silica-gel column (toluene/hexane) the final product was obtained as white solid (1.2 g, 96% Rdt). ^{1}H NMR (300 MHz, DMSO): 2.62 (s, 6H), 6.65–677 (m, 4H), 6.97–7.1 (m, 22H), 7.39 (dd, 2H, J = 6; J = 2.3), 7.96 (d, 2H, J = 8.8). ^{13}C NMR (75 MHz, $CDCl_3$): 124.68, 125.9, 126.62, 127.85, 127.93, 128.38, 128.4, 128.73, 130.88, 133.18, 133.31, 133.44, 134.34, 134.48, 134.63. ^{31}P NMR (81 MHz, $CDCl_3$): −14.7. $[\alpha]_D$ = +117.7 (c = 1, $CDCl_3$). HRLSIMS: MH^+. Calcd. 713.1588, found 713.1582. Mp: >300 °C. Calcd. C 84.9, H 5.5, P 9.5; found C 85.0, H 5.9, P 8.9.

2.8. (R)-5,5′-DimethylBINAPO (5′)

In a 250 mL round-bottomed flask were placed either (*R*)-5,5′-dimethylBINAP (**5**) (3 g, 4.6 mmol) and 100 mL of CH_2Cl_2. The mixture was cooled to 0 °C and 10 mL of hydrogen peroxide H_2O_2 (35%) then added. The mixture was stirred for 4 h. Then 100 mL of water was added. Aqueous phases were extracted with 50 mL of CH_2Cl_2. The organics phases were washed with 50 mL of aqueous sodium hydrogen sulfite solution, dried over Na_2SO_4, evaporated to obtained a brown solid (3.14 g, 4.8 mmol, quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): 2.75 (s, 6H), 6.7 (d, 2H, J = 14.7), 7.1–7.5 (m, 26H), 8.03 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 123.397, 123.653, 125.540, 125.760, 127.717, 127.896, 127.953, 128.035, 128.142, 130.937, 131.041, 131.993, 132.178, 132.445, 132.651. ^{31}P NMR (81 MHz, $CDCl_3$): 29.1. $[\alpha]_D$ = +112.4 (c = 1, DMF). ESI^+: MH^+ = 683.3. Mp: >300 °C. Calcd. C 80.9, H 55.3, O 4.6, P 9.0; found C 80.4, H 5.9, O 4.8, P 8.6.

2.9. (R)-5,5′-DiphenylBINAPO (7)

In a 250 mL round-bottomed flask under argon with a reflux condenser was placed, (*R*)-5,5′-dibormoBINAPO (**3**) (1 g, 1.23 mmol), phenyl boronic acid (450 mg, 3.69 mmol, 3 eq.), $Pd[(PPh_2)_4]$ (113.6 mg, 0.0984 mmol, 0.08 eq.), Na_2CO_3 (5 mL, 2M, degassed), EtOH (10 mL), DME (60 mL) was heated to reflux overnight. After cooled to room temperature, reaction mixture was filtered through celite and washed with CH_2Cl_2 (30 mL). The filtrate was washed three times with water and then dried on $MgSO_4$. LC separation on silica-gel column

(ETOAc/cyclohexane) giving pure product as yellow powder (quantitative yields). ^{1}H NMR (300 MHz, $CDCl_3$): 7.94 (d, 2H, $J = 13.0$), 6.6–7.39 (m, 38H). ^{13}C NMR (75 MHz, $CDCl_3$): 125.424, 126.98, 127.375, 127.824, 127.92, 128.06, 128.16, 128.29, 128.44, 130.3, 131.07, 131.96, 132.14, 132.25, 132.4, 132.61. ^{31}P NMR (81 MHz, $CDCl_3$): 28.99. $[\alpha]_D = +155.2$ ($c = 1$, DMF). ESI$^+$: $MH^+ = 807.3$. Mp: >300 °C. Calcd. C 83.3, H 5.0, O 3.9, P 7.6; found C 83.0, H 5.3, O 4.1, P 7.3.

2.10. (R)-5,5′-DiphenylBINAP (8)

In a 25 mL round-bottomed flask under an inert atmosphere fitted with a reflux condenser was placed, (*R*)-5,5′-diphenylBINAPO (**7**) (626 mg, 0.776 mmol), 10.5 mL of xylene and phenylsilane (3.9 mL, 31.06 mmol, 40 eq.) was added. The mixture is stirred 10 min at room temperature after 10 min the trichlorosilane (3.1 mL, 31.06 mmol, 40 eq.) was added dropwise, heated to 130 °C, after 15 h, the solution was cooled and stirred for 2 h, and NaOH (11 mL, 40%) was added very dropwise, the layer were separated, the aqueous phase washed with toluene (5 mL) and the organic layer were collected, washed with water, HCl, and water. After drying over $MgSO_4$ the solvent is removed to obtain a yellow solid (565 mg, 94%) ^{1}H NMR (300 MHz, $CDCl_3$): 6.84–7.49 (m, 38H), 7.8 (d, 2H, $J = 8.6$). ^{13}C NMR (75 MHz, $CDCl_3$): 125.66, 126.59, 127.64, 127.96, 128.04, 128.46, 128.6, 128.86, 130.67, 130.98, 133.24, 133.37, 133.5, 134.54, 134.7, 134.85. ^{31}P NMR (81 MHz, $CDCl_3$): −14.07. $[\alpha]_D = +60.3$ (*c* 1, DMF). HRLSIMS: MH^+. Calcd. 774.26, found 774.26. Mp: >300 °C. Calcd. C 86.8, H 5.2, P 7.9; found C 86.4, H 5.4, P 7.6.

2.11. Synthesis of methyl-Z-α-acetamidocinnamate (MAC)

This procedure is adapted from the literature [32]. A colourless solution of *N*,*N*′-dicyclohexyl-carbodiimide (DCC) (6.51 g, 31.5 mmole) was prepared from dissolution in DMF (2.5 mL) and addition of dichloromethane (10 mL). The mixture was then cooled to 13 °C. Using an addition funnel, a yellow solution of 5.02 g of α-acetamidocinnamic acid dissolves in 22 mL dichloromethane, 15 mL of methanol and 2.5 mL of DMF is added dropwise. After 5 min, a white precipitate formed. After 1 h at 15 °C, the solution is filtered and washed with 5 ml of dichloromethane. The solid (S1) will be reprocessed later. The filtrate is washed twice with hydrochloric acid (50 mL, 1 M) and the organic phase is dried over $MgSO_4$. The solution is filtered and evaporated to give a yellow solid which is redissolved in DMF (10 mL). The solution is left for 2 days to yield a white precipitate of *N*,*N*′-dicyclohexylurea (DCU). After filtration, the solution is evaporated to give an orange oil which is dissolved in the minimum of methanol and an identical volume of diethylether. The solution is frozen for recrystallization. The recrystallization is conducted three times for a yield of 52%.

2.12. Catalysts: [Rh(BINAP derivatives)(COD)]BF_4

Stock solutions of [Rh(BINAP derivatives)(COD)]BF_4 catalysts were prepared in a glove box under argon by stirring a mixture of $[Rh(COD)_2]BF_4$ (1 eq. mmol) and BINAP derivatives (1.05 eq. mmol) in degassed methanol at room temperature during 1 h. They were stored at 0 °C before use. $^{31}P\{^{1}H\}$ (81 MHz) NMR of the so prepared solutions displayed the expected features: [RhCOD(R-BINAP)][BF_4] (CD_3OD; δ ppm 26.3 (d); $J_{PRh} = 147$ Hz); [RhCOD(*R*-5,5′-DiMeBINAP)][BF_4] ($CDCl_3$; δ ppm 25.7 (d); $J_{PRh} = 146$ Hz); [RhCOD(*R*-5,5′-DiBrBINAP)][BF_4] ($CDCl_3$; δ ppm 26.3 (d); $J_{PRh} = 148$ Hz); [RhCOD(*R*-5,5′-diacideBINAP)][BF_4] (CD_3OD; δ ppm 26.3 (d); $J_{PRh} = 147$ Hz); [RhCOD(*R*-5,5′-diperfluoroBINAP)][BF_4] ($CDCl_3$; δ ppm 26.3 (d); $J_{PRh} = 148$ Hz); [RhCOD(*R*-5,5′-dicyanoBINAP)][BF_4] (CD_2Cl_2; δ ppm 25 (d); $J_{PRh} = 137$ Hz); [RhCOD(*R*-5,5′-DiPhBINAP)][BF_4] ($CDCl_3$; δ ppm 26 (d); $J_{PRh} = 148$ Hz).

3. Hydrogenation

A solution of **1a** (**1b**) (0.1 M) in MeOH (4 mL) was stirred (2200 rpm) at 35 °C with the catalyst [Rh(BINAP derivatives)(COD)]BF_4 (10^{-3} or 10^{-4} M) under H_2 (5 or 30 bar). The conversion and enantiomeric excess (ee ± 1%) were determined from on time sampling of the reaction mixture by GC analysis on lipodex A (25 m × 0.25 mm) and CHIRASILVAL (25 m × 0.25 mm) columns.

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