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Diastereo- and Enantioselective Hydrogenation of a Challenging Enamide Derived from 4-Phenyl-2-tetralone: An Appealing Shortcut Towards Enantiopure *cis*-2-Aminotetraline Derivatives

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Dedicated to the 150th anniversary of Japan–UK diplomatic relations

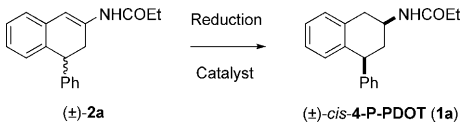
Abstract: A clean, efficient, and diasteroselective ($dr > 95\%$) catalytic hydrogenation of the enamide *N*-(4-phenyl-3,4-dihydronaphthalen-2-yl)propionamide (**2a**) using palladium on carbon is performed. This procedure provides the melatonin receptor ligand (±)-*cis*-4-phenyl-2-propionamidotetralin (*cis*-4-P-PDOT, **1a**) and its 8-methoxy analog. Furthermore, Rh and Ru catalyzed homogeneous asymmetric hydrogenation of the challenging racemic endocyclic enamide **2a** with several chiral phosphine ligands is studied. The best results, in terms of enantioselectivity, for both diastereomers are obtained when chiral Rh-Josiphos is used as the catalyst.

Keywords: asymmetric synthesis · diastereoselectivity · enamides · hydrogenation · rhodium

Introduction

The reduction of organic compounds is perhaps the most common type of reaction used in organic synthesis.[1] Unquestionably, hydrogen is the cleanest reducing agent and hydrogenation is the most important heterogeneous and homogeneous catalytic method used in synthetic organic chemistry both on a laboratory and an industrial scale.[2] Recently, asymmetric hydrogenation of prochiral functionalized olefins, ketones, and imines, has been shown to be one of the most effective and powerful methods for the synthesis of chiral compounds in numerous applications.[3] Among functionalized olefins, enamides, which are stable enamine surrogates,[4] have gained particular attention as useful intermediates for the preparation of many biologically active amines with high optical purity.[5] Recently, we have reported a convenient protocol for the gram-scale synthesis of one of the most interesting melatonin MT_2 selective ligand, (±)-*cis*-*N*-(4-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (*cis*-4-P-PDOT, *cis*-**1a**).[6] The synthesis involved the ionic reduction of the cyclic enamide, (±)-*N*-(4-phenyl-3,4-dihydronaphthalen-2-yl)propionamide (**2a**) with Et_3SiH (TES) in trifluoroacetic acid (TFA) as the key step. We now describe a more complete study of the diasteroselective reduction of enamide **2a** using different reducing agents (hydrides and hydrogen) (Scheme 1). Moreover, as *cis*- and *trans*-4-P-PDOT display different MT_2 binding affinities (pKi 10.80 vs. 8.45, respectively),[7] it would be particularly interesting to synthesize both *cis*-enantiomers to find out the eutomer. Among all of the possible approaches, asymmetric catalysis is the method of choice for the synthesis of enantiopure compounds. In particular, transition metal-catalyzed asymmetric hydrogenation is now the most reliable and widely used synthetic tool for rapid access to optically active molecules.[8] Accordingly, asymmetric catalytic hydrogenation of trisubstituted endocyclic enamide **2a** has been envisioned (Scheme 1).

Despite the fact that 4-substituted-2-aminotetraline derivatives display several interesting medicinal properties,[9] a lit-



(±)-**2a** (±)-*cis*-**4-P-PDOT** (**1a**)

Scheme 1. Key step to the synthesis of MT_2 selective ligand *cis*-4-P-PDOT (**1a**).

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erature search revealed a surprising lack of precedents on the use of hydrogenation (asymmetric and symmetric) as a synthetic approach to the target structures. It appears that even the cyclic enamides and encarbamates derived from 4-unsubstituted-2-tetralone are very challenging substrates employed as standards for testing new asymmetric hydrogenation methods. There are only a few ruthenium-[10] and rhodium-based[11] catalysts known to reduce these molecules with moderate to good enantioselectivities. Only one example, reported by the Reek group, claimed a 94% *ee* for the reduction of commercially available *N*-(3,4-dihydro-naphthalen-2-yl)acetamide by a rhodium-based supramolecular catalyst. A combinatorial approach combined with high-throughput screening technique was used in this study.[11e] The trisubstituted endocyclic enamide **2a**, which contains a stereogenic carbon center, is an even more complicated substrate and requires a catalytic system that can overcome the intrinsic substrate bias. In other words, the optimal catalyst would potentially yield 50% of both enantiopure *cis*- and *trans*-4-P-PDOT.[12]

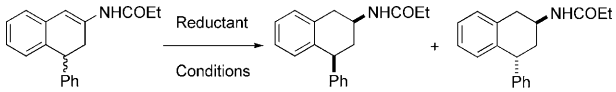
With all of this in mind, herein we document the optimization of the diastereoselective reduction of the racemic enamide **2a** and the first preliminary studies towards its enantioselective hydrogenation using ruthenium- and rhodium-based catalysts.

Results and Discussion

The most significant results obtained for the diastereoselective reduction of enamide **2a** are reported in Table 1.

First, we tried to improve the diastereoselectivity and identify more viable reaction conditions for the reduction of enamide **2a**. The reported ionic reduction using TES worked at −10°C in TFA, to afford the desired *cis*-4-P-PDOT in 91% yield and 4:1 diastereoselectivity (entry 2).[6] However, the reaction needed a strong Bronsted acid as a solvent and proceeded slowly in the presence of a co-solvent and/or with a decrease in the temperature (entries 1 and 3). This would preclude application to more sensitive substrates, as well as an asymmetric approach. When we attempted to replace the TFA with a catalytic amount of Lewis acid, such as $Sc(OTf)_3$ (entry 4), $Bi(OTf)_3$, and $InCl_3$, only trace amounts of product were obtained. Using different silanes (entries 5 and 6), the reaction worked smoothly to give the corresponding product with results comparable to those obtained on using only TFA as the solvent. Interestingly, sterically hindered tris(trimethylsilyl)silane lowered the *cis*/*trans* ratio ($dr = 63\%$). We also tried the reaction with other hydride reducing agents. Sodium borohydride, sodium cyanoborohydride (entry 7), and sodium triacetoxy borohydride worked well in the presence of TFA with results similar to using TES. Lithium borohydrides (superhydride and L-selectride), lithium aluminum hydrides, alanes, and borane either gave complicated reaction mixtures or did not work at all. As expected, upon using stronger hydride donors, the amide moiety interferes with the double bond reduction and so the corresponding amine and tetralone **3a** were the main products. Tetralone **3a** was also obtained when zinc powder in TFA was used as the reducing agent at 80°C for 16 h (entry 10). One possible explanation could be that the amide moiety was first reduced to give the enamine intermediate, which then hydrolyzed to the tetralone. Trace amounts of **1a** were also obtained while using Hantzsch ester in TFA (entry 11), whereas using a thiourea derivative as a substoichiometric Bronsted acid in chloroform did not work at all (entry 12). On the contrary, a quantitative yield of *cis*-4-P-PDOT with a 95% diastereomeric ratio was obtained in only 5 min using hydrogen (4 atm) with a catalytic amount of palladium on carbon (10%) at room temperature (entry 13). The Pd-catalyzed hydrogenation of enamide **2a** improved the total yield for the three step synthesis of *cis*-4-P-PDOT from 38% to 51% (see Scheme 2). This synthetic approach was also applied to the synthesis of a new melatonin receptor tetralin ligand (**1b**) that bears a methoxy substituent in a position topologically equivalent to the 5-methoxy group of melatonin, essential for biological activity. In this case, in order to obtain the tetralone **3b**, we needed to change the order of addition of the reagents.[13] We speculated that 2-methoxyphenylacetyl chloride

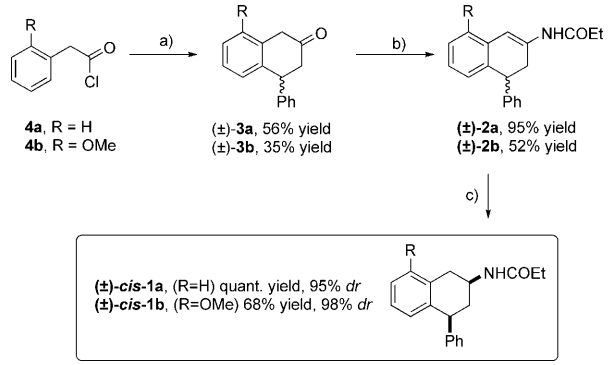
Table 1. Optimization of diastereoselective reduction of racemic **2a**.



(±)-**2a** (±)-*cis*-**4-P-PDOT** (±)-*trans*-**4-P-PDOT**

Entry	Reductant	Conditions	Yield[a]	*dr cis*/*trans*[b]
1	TES[c]	CH_3COOH, RT,16 h	n.r.[d]	–
2	TES[c]	CF_3COOH, −10°C, 20 min	91	81:19
3	TES[c]	CF_3COOH/MeOH, −78°C, 5 h	trace	–
4	TES[c]	$Sc(OTf)_3$, CH_2Cl_2, RT, 16 h	trace	–
5	Me_2PhSiH	CF_3COOH, RT, 20 min	97	71:29
6	$(Me_3Si)_3SiH$	CF_3COOH, RT, 20 min	98	63:37
7	$NaCNBH_3$	CF_3COOH/MeOH, 0°C, 16 h	95	80:20
8	L-selectride[e]	THF, RT, 16 h	n.r.[d]	–
9	Red-Al[f]	THF, RT, 16 h	–[g]	–
10	Zinc powder	CF_3COOH, 80°C, 16 h	–[h]	–
11	Hantzsch ester[i]	CF_3COOH, RT, 16 h	trace	–
12	Hantzsch ester[i]	Thiourea[j], $CHCl_3$, RT, 16 h	n.r.[d]	–
13	H_2 (4 atm)	10% Pd/C, MeOH, RT, 5 min	>99	95:5

[a] Yield of isolated product. [b] Determined by HPLC and confirmed by ^1H NMR. [c] Triethyl silane. [d] No reaction. [e] Li(*sec*-Bu)$_3$BH 1 M solution in THF. [f] $Na(MeOCH_2CH_2O)_2AlH_2$ 1 M solution in THF. [g] Enamine and amine derived from the reduction of **2a** were also observed together with the starting material by HPLC-MS analysis. [h] Tetralone **3a** was the main product by HPLC-MS analysis. [i] Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. [j] 1,3-bis[3,5-bis(trifluoromethyl)-phenyl]thiourea, (30%).



Scheme 2. Synthesis of (±)-*cis*-**1a** and **1b**. Reagents and conditions: a) styrene, $AlCl_3$, CH_2Cl_2, 0 °C, 30–45 min; b) Propionamide, PTSA (10 %), toluene, reflux using Dean–Stark apparatus, 2–3 h; c) H_2 (4 atm), Pd/C (10 %), MeOH, RT, 5–10 min.

in the presence of a Lewis acid may undergo a self Friedel–Craft acylation or, more likely, the $AlCl_3$ may coordinate to the more basic methoxy group, and thus lower the yield of the reaction.

Given the excellent results obtained for the heterogeneous catalytic hydrogenation experiments, we decided to try asymmetric approaches. The homogeneous hydrogenation of enamide **2a** at 1 atm using $Rh(COD)_2BF_4$ (10 %) and PPh_3 (20 %) (at room temperature for 14 h) gave the corresponding product in quantitative yield with a diastereomeric ratio of 72 %.

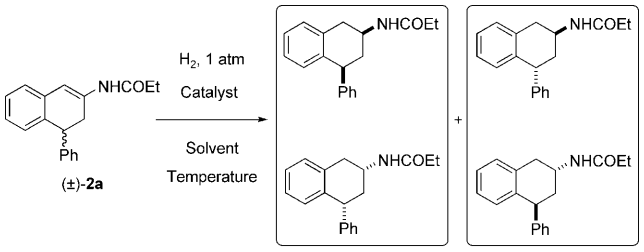
As the homogeneous Rh-catalysis was less affected by the intrinsic substrate bias and slower than the heterogeneous Pd/C-catalysis, we explored other combinations of metals and ligands. The first chiral ligand tested was the well-known bisphosphine (*R*)-(+)-BINAP, and the results are reported in Table 2.

Different solvents, temperatures, reaction times and catalyst loadings were evaluated using the Rh-based catalyst. The solvent played a role in the reaction and dichloromethane gave the highest yield and enantioselectivity values for both *cis* and *trans* isomers. A decrease in the temperature caused the reaction to slow down and after 24 h at 0 °C, only 10 % conversion was obtained with similar selectivity (entry 5). Hydrogenation with a preformed (*S*)-BINAP-$RuBr_2$[16] catalyst required a higher pressure of hydrogen to give acceptable conversion (entry 6 vs. entry 7). In addition, a strong 4-phenylsubstituent bias gave predominately the *cis*-diastereomer.

Several rhodium–phosphine complexes have been developed as efficient catalysts for the asymmetric hydrogenation of acyclic enamides but only limited success has been achieved for the hydrogenation of cyclic enamides. Therefore, the asymmetric hydrogenation of the cyclic enamide **2a** with several rhodium-ligand complexes was explored. Rational selection of the commercially available chiral phosphines was done on the basis of different factors, such as monodentate or bidentate, steric–electronic effects, bite angle and C_1 or C_2 symmetry for bidentate ligands, and chirality on the backbone or on phosphorus atoms. The most interesting results are reported in Table 3. As expected, C3-Tunephos gave results comparable to the BINAP-Rh-based hydrogenation, whereas the monodentate phosphine Ph-BINEPINE gave low enantioselectivity values. On the contrary, the commercially available monodentate phosphoramidate, MONOPHOS, was unreactive. Bisphosphine ligands seem to be essential in order to achieve enantioselectivity. However, the central chiral-based bisphosphines, TANGPHOS, Me-DUPHOS, and Quinoxaline did not provide the corresponding product with good enantioselectivity.

We were delighted to find that the C_1 symmetrical Josiphos (*R*,*S*)-PPF-P*t*Bu_2-Rh-based catalyst worked well and gave amide **1a** in excellent yield and agreeable *ee* values (64 % and 76 % *ee* for the *cis* and *trans* isomers, respectively).[14] Even though the procedure is still not optimal, these results encourage further studies.

Table 2. (*R*)-BINAPRhBF_4 and (*S*)-BINAPRuBr_2 hydrogenation of racemic **2a**.



Entry	Catalyst	*T* [°C], *t* [h]	Solvent	Yield[a]	*dr*[b]	*ee*[b]	
						cis	*trans*
1	(*R*)-BINAP**Rh**BF_4	45, 48	MeOH	95	69	17	38
2		40, 20	Toluene	74	79	17	57
3		35, 22	THF	88	74	19	53
4		35, 18	CH_2Cl_2	98	57	35	50
5		0, 24		10	50	35	50
6	(*S*)-BINAP**Ru**Br_2	35, 16	MeOH	15	91	65	53
7[c]		50, 16		69	97	49	50

[a] Yield of isolated product. [b] *cis*/*trans* and *ee* ratio were determined by chiral HPLC. [c] The reaction was performed with H_2 at 6 atm.

Conclusions

We have reported an almost complete diastereoselective hydrogenation of endocyclic enamides derived from 4-phenyl-2-tetralone using heterogeneous palladium catalyzed hydrogenation to give the racemic melatonin ligand *cis*-4-P-PDOT in a cleaner, easier, and scalable way. We have also reported the asymmetric hydrogenation studies of the trisubstituted endocyclic chiral enamide **2a** to provide *cis*-4-P-PDOT and *trans*-4-P-PDOT with 64 % and

Table 3. Rh-based enantioselective hydrogenation of racemic **2a**.[a]

Phosphine	Chirality	Yield[b]	*dr*[c] *cis*/*trans*	*ee*[c] *cis*	*trans*
(*R*)-C3-TUNEPHOS	Axial	92	60	32	53
(*S*)-Ph-BINEPINE[d]		92	82	7	10
(*R*)-MONOPHOS[d]		trace	–	–	–
(*S*,*S*,*R*,*R*)-TANGPHOS	Central	89	57	24	41
(*R*,*R*)-Me-DUPHOS		71	74	6	64
(*R*,*R*)-(*t*-BMP)-QUINOXALINE		85	62	1	22
(*S*,*S*)-Et-FERROTANE	Planar	95	59	20	19
Josiphos (*R*,*S*)-PPF-P*t*Bu$_2$	+	98	52	64	76
Josiphos (*R*,*S*)-cy$_2$PF-P*t*Bu$_2$	Central	91	49	26	24
Josiphos (*R*,*S*)-PPF-Pxyl$_2$		79	64	13	29

[a] Reaction conditions: [Rh(COD)$_2$BF$_4$]-chiral phosphine (1:1.1, 10% cat. loading), H_2 (1 atm), 35 °C, CH_2Cl_2, 16 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Rh/monodentate ligand = 1:2.1 ratio was used.

76% *ee*, respectively, using the Rhodium-(*R*,*S*)-PPF-P*t*Bu$_2$ Josiphos catalytic system. This is the first example of enantioselective hydrogenation of an enamide derived from 4-substituted-2-tetralones, a scaffold widely employed in medicinal chemistry. Biological studies on the enantio-enriched *cis*- and *trans*-4-P-PDOT are now underway and the results will be reported in the near future.

Experimental Section

General Methods

Melting points were determined on a Büchi B-540 capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 200 spectrometer, using $CDCl_3$ as solvent unless otherwise noted. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). ESI-MS spectra were recorded on a Waters Micromass ZQ instrument. Only molecular ions (M+1) are given. High-performance liquid chromatography was carried out on the following apparatus: Shimadzu LC-10AT (liquid chromatograph), Shimadzu SPD-10A (UV detector), and Shimadzu C-R6A Chromatopac. Infrared spectra were obtained on a Nicolet Avatar 360 FTIR spectrometer, and the transmittance is reported in cm^{-1}. Column chromatography purifications were performed under "flash" conditions using Merck 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates and preparative thin-layer chromatography was carried out using Merck silica gel 60 F_{254} 0.5 mm PTLC plates (20×20 cm). All chemicals were purchased from commercial suppliers and used directly without any further purification.

Syntheses

(±)-8-Methoxy-4-phenyl-3,4-dihydronaphthalen-2(1*H*)-one (3b): Anhydrous aluminium trichloride (1.6 g, 12 mmol) was added to a solution of freshly distilled styrene (0.69 mL, 6 mmol) and 2-methoxyphenylacetyl chloride[15] (1.1 g, 6 mmol) in dry CH_2Cl_2 (100 mL) under nitrogen at 0 °C. The resulting mixture was stirred at 0 °C for a further 15 mins and then quenched by a saturated solution of Seignette salt (100 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (3×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude tetralone **3b**, which was purified by flash chromatography (silica gel, cyclohexane/EtOAc = 9:1) to give an oil (35% yield). R_f = 0.3 (cyclohexane/EtOAc = 9:1); UV/Vis (MeOH): λ_{max} = 271, 279 nm; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.94 (d, ^3J(H,H) = 6.2 Hz, 2H, CH_2), 3.59 (m, 2H, CH_2), 3.87 (s, 3H, OMe), 4.47 (t, ^3J(H,H) = 6.2 Hz, 1H, $CHPh_2$), 6.66 (d, ^3J(H,H) = 7.7 Hz, 1H, ArH), 6.81 (d, ^3J(H,H) = 8.1 Hz, 1H, ArH), 7.08–7.35 ppm (m, 6H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 38.2, 45.4, 46.5, 55.4, 108.4, 120.6, 122.2, 126.9, 127.4, 127.8, 128.8, 139.9, 142.2, 156.8, 209.5 ppm; MS (ESI): m/z (%): 253 (100) [M+1]; elemental analysis: calcd (%) for $C_{17}H_{16}O_2$ (252.3): C 80.93, H 6.39; found: C 80.78, H 6.35.

(±)-*N*-(8-Methoxy-4-phenyl-3,4-dihydronaphthalen-2-yl)propionamide (2b): A solution of tetralone **3b** (1.72 g, 6.8 mmol), propionamide (1.2 g, 16.4 mmol), and *p*-toluene sulfonic acid (0.13 g, 0.7 mmol) in toluene (30 mL) was refluxed for 4 h under nitrogen atmosphere in a 50 mL round-bottom flask equipped with a Dean Stark apparatus. After cooling to room temperature, the unreacted propionamide precipitated, was filtered off, and washed with cold toluene (2×2 mL). The resulting organic phase was washed with a saturated solution of $NaHCO_3$ (3×50 mL) and water (3×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude enamide **2b** was purified by flash chromatography (silica gel, cyclohexane/EtOAc = 7:3) followed by crystallization to give a white solid (52% yield). R_f = 0.32 (cyclohexane/EtOAc = 7:3); m.p.: 195–6 °C (acetone/Et_2O); UV/Vis (MeOH): λ_{max} = 262, 269 nm; IR (nujol): $\tilde{\nu}$ = 3344 (N–H), 1662 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.18 (t, ^3J(H,H) = 7.4 Hz, 3H, $NHCOCH_2CH_3$), 2.29 (q, ^3J(H,H) = 7.4 Hz, 2H, $NHCOCH_2CH_3$), 2.68–2.95 (m, 2H, $C3H_2$), 3.85 (s, 3H, OMe), 4.18 (dd, ^3J(H,H) = 7.3, 8.7 Hz, 1H, $CHPh_2$), 6.44 (d, ^3J(H,H) = 7.6 Hz, 1H, ArH), 6.54 (br s, 1H, NH), 6.74 (d, ^3J(H,H) = 8.2 Hz, 1H, ArH), 7.00 (dd, ^3J(H,H) = 7.6, 8.1 Hz, 1H, ArH), 7.20–7.35 ppm (m, 6H, ArH + C1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.5, 30.8, 35.3, 44.4, 55.5, 109.0, 120.0, 123.6, 126.4, 126.6, 128.3, 128.5, 130.0, 133.0, 136.5, 143.6, 154.7, 172.1 ppm; MS (ESI): m/z (%): 308 (100) [M+1]; elemental analysis: calcd (%) for $C_{20}H_{21}NO_2$ (307.4): C 78.15, H 6.89, N 4.56; found: C 78.26, H 6.86, N 4.53.

General procedure for Pd/C catalytic hydrogenation of enamides 2a and 2b: A solution of enamide (0.5 mmol) in methanol (12 mL) was hydrogenated over 10% Pd/C (14 mg) at 4 atm of H_2 for 5–10 min at room temperature. The catalyst was filtered off over a celite plug and washed with methanol (3×5 mL). The filtrate was concentrated under reduced pressure to afford the crude tetraline which was directly purified by crystallization.

(±)-*cis*-*N*-(4-Phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (1a): The physical-chemical properties were identical with those previously reported.[7]

(±)-*cis*-*N*-(8-Methoxy-4-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propionamide (1b): White solid (68% yield). m.p.: 220–2 °C (acetone/*n*-hexane); R_f = 0.35 (dichloromethane/acetone = 95:5); IR (nujol): $\tilde{\nu}$ = 3336 (N–H), 1646 cm^{-1} (C=O); UV/Vis (MeOH): λ_{max} = 273, 281 nm; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.15 (t, ^3J(H,H) = 7.6 Hz, 3H, $NHCOCH_2CH_3$), 1.75 (apt q, J(H,H) = 11.9 Hz, 1H, C3Ha), 2.18 (q, ^3J(H,H) = 7.6 Hz, 2H, $NHCOCH_2CH_3$), 2.35–2.49 (m, 2H, C3Hb+C1Ha), 3.34 (dd, ^2J(C1Hb,C1Ha) = 16.0 Hz, ^3J(C1Hb,C2H) = 5.4 Hz, 1H, C1Hb), 3.84 (s, 3H, OMe), 4.24 (dd, ^3J(H,H) = 5.1, 11.2 Hz, 1H, C4H), 4.32–4.36 (m, 1H, C2H), 5.44 (br d, ^3J(H,H) = 7.8 Hz, 1H, NH), 6.40 (d, ^3J(H,H) = 7.8 Hz, 1H, ArH), 6.69 (d, ^3J(H,H) = 8.1 Hz, 1H, ArH), 7.03 (dd, ^3J(H,H) = 7.8, 8.1 Hz, 1H, ArH), 7.22–7.34 ppm (5H, m, ArH); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.9, 29.9, 30.7, 39.9, 45.5, 46.2, 55.3, 107.2, 121.6, 124.1, 126.4, 128.4, 128.5, 128.6, 140.1, 146.0, 156.9, 173.1 ppm; MS (ESI): m/z (%): 310 (100) [M+1]; elemental analysis: calcd (%) for $C_{20}H_{23}NO_2$ (309.4): C 77.64, H 7.49, N 4.53; found: C 77.59, H 7.47, N 4.51.

General procedure for the Rhodium-catalyzed asymmetric hydrogenation of enamide 2a: A Schlenk tube placed in a glove box was charged with the opportune chiral ligand (0.027 mmol, 0.11 eq), bis(cyclooctadiene)rhodium tetrafluoroborate [Rh(COD)$_2$BF$_4$] (9.7 mg, 0.024 mmol, 0.10 eq), and the enamide **2a** (67 mg, 0.242 mmol, 1 eq). The tube was then taken out from the glove box and charged with the appropriate degassed solvent (4 mL) under argon. The resulting mixture was stirred for 15 min at 35 °C and the solution color turned to yellow-brown. The argon atmosphere was replaced with hydrogen (1 atm) and the reaction was stirred at a suitable temperature until completion. The reaction mixture was filtered over a celite plug and the solvent was removed under reduced pressure. Diastereomeric ratio and enantiomeric excess were determined by

HPLC on a Chiralcel (Chiralpak) AD-H column, with hexane/*i*PrOH = 19:1 as eluent, flux 1.0 mL min^{-1}, λ = 262 nm; *trans*-4-P-PDOT: t_r1 = 10.8 min, t_r2 = 14.5 min; *cis*-4-P-PDOT: t_r1 = 17.5 min, t_r2 = 21.7 min. The crude material was purified by flash chromatography (silica gel, cyclohexane/EtOAc = 7:3) to afford the *cis*- and *trans*-4-P-PDOT as a mixture (yield of isolated product, see Tables 2 and 3). A little amount of pure *cis*-4-P-PDOT and *trans*-4-P-PDOT were obtained by purification of the diastereomeric mixture using preparative thin layer chromatography (dichloromethane/acetone = 95:5).[7]

Procedure for the (*S*)-BINAPRuBr$_2$[16] catalyzed asymmetric hydrogenation of enamide 2a: A Schlenk tube placed in a glove box was charged with (*S*)-BINAP (16 mg, 0.024 mmol, 0.10 eq) and (cyclooctadiene)-bis(2-methylallyl)ruthenium [Ru(COD)(MA)$_2$] (8.0 mg, 0.024 mmol, 0.10 eq). The tube was then taken out from the glove box and charged with degassed and anhydrous acetone (4 mL) under argon. To this suspension, a solution of HBr (0.22 mL, 0.29 M solution prepared by diluting 48% aq HBr in MeOH) was added and the suspension was stirred at room temperature for 30 min. A yellow solid precipitated. The mixture was evaporated under vacuum and the resulting catalyst was immediately used. The enamide **2a** (67 mg, 0.24 mmol, 1 eq) in anhydrous and degassed MeOH (4 mL) was successively added to the catalyst. The argon atmosphere was replaced with hydrogen and the reaction was stirred at the suitable temperature for 16 h. The reaction mixture was filtered over a celite plug and the solvent was removed under reduced pressure. Diastereomeric ratio, enantiomeric excess, and isolated yield were determined as reported above.

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