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Synthesis of Enantiomerically Pure 1,2,3,4-Tetrahydro-β-carbolines and *N*-Acyl-1-aryl Ethylamines by Rhodium-Catalyzed Hydrogenation

Stephan Enthaler,[a] Giulia Erre,[a] Kathrin Junge,[a] Daniele Addis,[a] Renat Kadyrov,[b] and Matthias Beller*[a]

Abstract: The rhodium-catalyzed asymmetric hydrogenation of different enamides, in particular, dihydro-β-carboline derivates, was investigated in the presence of chiral phosphorus ligands. Enantioselectivities of up to 99% *ee* were obtained after ligand screening and optimization of the reaction conditions. The scope and limitation of the catalysts were shown in the synthesis of optically active tetrahydro-β-carbolines and other benchmark *N*-acyl-1-aryl ethylamines.

Keywords: asymmetric hydrogenation · enamides · homogeneous catalysis · hydro-β-carbolines · phosphane ligands

Introduction

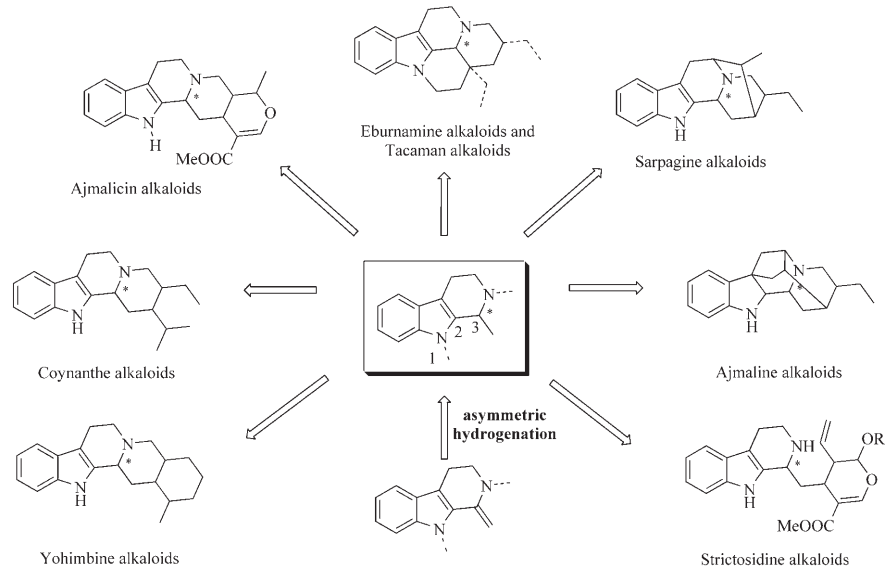
There is a growing trend to substitute traditional stoichiometric transformations by more environmentally benign catalytic processes in the synthesis of natural products and novel biologically active compounds. Catalysis often allows us to access new reaction types, to decrease the number of reaction steps, and to improve waste balance, because of high atom efficiency and selectivity as well as tolerance of a broad range of functional groups.[1] For example, catalytic methods have been shown to improve the synthesis of indoles, which is one of the most represented building blocks in natural bioactive products and marketed drugs.[2,3] Scheme 1 shows a selection of indol alkaloids with the tetrahydro-β-carboline skeleton. A crucial structural element of all the compounds shown is the chiral carbon atom at the 3-position (Scheme 1).

To date, relatively few catalytic attempts have been carried out to introduce chirality in the 3-position. For instance, asymmetric Pictet–Spengler reactions catalyzed by chiral Brønsted acids[4] or chiral boranes,[5] proline-catalyzed asymmetric addition of ketones to dihydro-β-carbolines,[6] and asymmetric hydrogenations have been reported.[7,8,9] Among the different catalytic approaches, asymmetric hydrogenation offers probably the most versatile and elegant tool with respect to selectivity, generality, and atom efficiency. So far, both catalytic transfer hydrogenation and hydrogenation with molecular hydrogen were established by Noyori and co-workers,[7] Morimoto et al.,[8] and others[9] for the synthesis of tetrahydro-β-carboline and isoquinolines.[10] Hence, ruthenium-catalyzed transfer hydrogenation of dihydro-β-carboline imines in the presence of Noyori or Noyori-based catalysts gave enantioselectivities of >99% *ee* with formic acid as the hydrogen source.[7,9] Furthermore, Morimoto et al. reported the catalytic reduction of similar substrates with molecular hydrogen in the presence of iridium diphosphane complexes, whereby an enantioselectivity of up to 95% *ee* was attained.[8]

Comparing the different catalytic possibilities for the preparation of enantiomerically pure tetrahydro-β-carbolines, we thought that the asymmetric hydrogenation of the corresponding enamide precursors offers an attractive synthetic approach. On the basis of our own work in catalytic hydrogenation[11] and inspired by the successful application of different enamide hydrogenation protocols within the last 30 years, which utilize bidentate as well as monodentate phosphorus ligands,[6] we report herein for the first time effective catalysts for such reductions.

[a] Dr. S. Enthaler, G. Erre, Dr. K. Junge, D. Addis, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse an der Universität Rostock e. V.
Albert-Einstein-Str. 29A
D-18059 Rostock (Germany)
Fax: (49) 381–1281–5000
E-mail: matthias.beller@catalysis.de

[b] Dr. R. Kadyrov
Evonik-Degussa AG
Rodenbacher Chaussee 4
D-63457 Hanau (Germany)



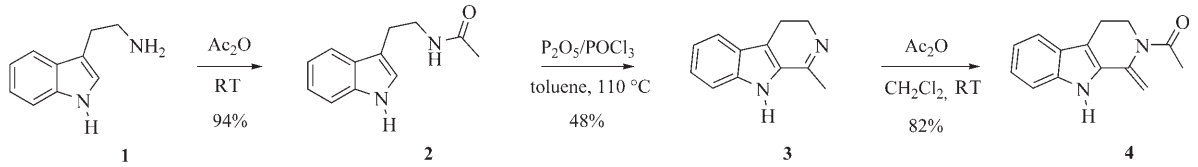
Scheme 1. Examples of indol alkaloids based on the tetrahydro-β-carboline framework.

Results and Discussion

The model substrate **4** for the catalytic hydrogenation studies was synthesized by acylation of tryptamine **1** with neat acetic anhydride, subsequent ring formation by Bischler–Napieralski reaction in the presence of a $P_2O_5/POCl_3$ mixture,[14] and finally double-bond shift to the exocyclic position by acetylation of the formed imine **3** with acetic anhydride[15] (Scheme 2). Here, the overall yield for enamide **4** was 37%.

With substrate **4** in hand, we initially carried out an evaluation of potentially suitable ligands for the rhodium-catalyzed asymmetric hydrogenation. The catalytic reactions were performed with a precatalyst composed of 1.0 mol% $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) and 1.0 mol% of the corresponding ligand (2.1 mol% for monodentate ligands) in dichloromethane and an initial hydrogen pressure of 2.5 bar.[16] Selected results from this study are presented in Table 1. In all cases, good to excellent yields were achieved within 24 h. Specifically, if the chelating diphosphane ligands are subdivided into four coordination modes (five-, six-, seven-, and nine-membered rings, based on phosphorus–metal–phosphorus), good enantioselectivities were displayed for seven-membered-ring systems (Table 1, entries 1–3), whereas six- and nine-membered-ring ligands showed only poor enantioselectivity (Table 1, entries 6 and 15). In the case of five-membered-ring chelating systems, the best enantioselectivity of up to 96% *ee* was obtained with the phospholane-based diphosphane cat*A*Sium MNXyF ligand **16**[17] (Table 1, entry 12). The structurally similar Me-DuPhos attained significantly lower enantioselectivity (Table 1, entry 10). We also examined monodentate phosphorus ligands, for example, MonoPhos **17** and Ph-Binepine **18**, which have been proven to be highly active in the asymmetric hydrogenation of enamide structures; however, only moderate to good enantioselectivities were observed here (Table 1, entries 13 and 14). Notably, the enantioselectivity was improved to 62% *ee* when the phenyl group of Ph-Binepine was replaced by a *tert*-butyl group, whereas in most other benchmark tests the latter showed inferior stereoselection.[11c–g,18]

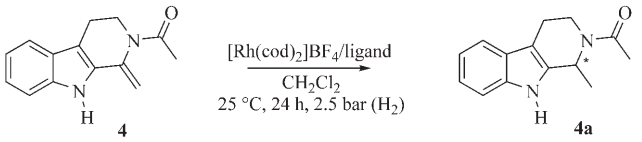
Since the phospholane-based diphosphane cat*A*Sium MNXyF **16** showed promising results in the asymmetric hydrogenation of compound **4**, structurally similar ligands were tested in more detail in this reaction (Table 2).[17] However, substitution at the nitrogen atom with different groups



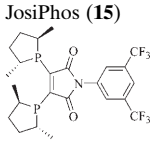
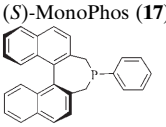
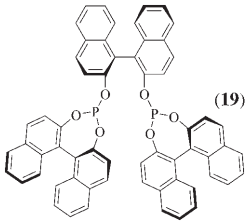
Scheme 2. Synthesis of 1-(1-methylene-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)ethanone (**4**).

Abstract in German: Im Rahmen dieser Arbeit wird die Rhodium-katalysierte asymmetrische Hydrierung von Enamiden vorgestellt, wobei ein besonderes Augenmerk auf der Synthese von Vorstufen für Indolalkaloide (1,2,3,4-Tetrahydro-β-carboline) lag. Nach Untersuchung verschiedenster Ligandensysteme und Optimierung der Reaktionsbedingungen konnten Enantioselektivitäten von bis zu 99% *ee* erzielt werden. Dabei erwiesen sich Phospholan-basierte Diphosphane als besonders geeignet zum Chiralitätstransfer. Die hervorragenden Eigenschaften dieser Ligandklasse konnte weiterhin in der asymmetrischen Hydrierung verschiedenster Enamide erfolgreich gezeigt werden.

Table 1. Asymmetric hydrogenation of enamide **4** with various phosphorus ligands.[a]

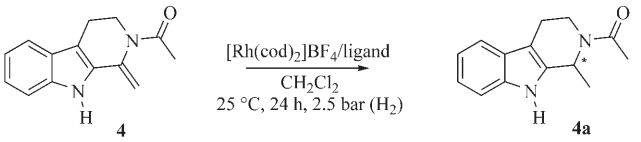


4 **4a**

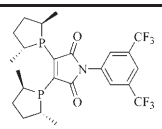
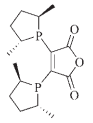
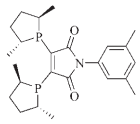
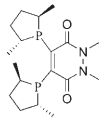
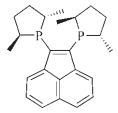
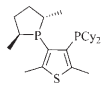
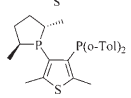
Entry	Ligand	Conv. [%]	*ee* [%]
1	(*R*,*R*)-diop (**5**)	94	85 (−)
2	(*S*)-binap (**6**)	94	92 (−)
3	(*R*)-Tolbinap (**7**)	>99	90 (+)
4	(*S*,*S*)-ChiraPhos (**8**)	62	94 (−)
5	(*S*,*S*)-bppm (**9**)	81	rac.
6	(*S*,*S*)-bdpp (**10**)	>99	rac.
7	(*S*,*S*)-DeguPhos (**11**)	99	rac.
8	(*R*,*R*)-PyrPhos (**12**)	91	68 (+)
9	(*S*,*S*)-Et-FerroTane (**13**)	>99	86 (+)
10	(*S*,*S*)-Me-DuPhos (**14**)	>99	86 (+)
11	JosiPhos (**15**)	99	76 (+)
12	 (**16**)	>99	96 (−)
13	(*S*)-MonoPhos (**17**)	98	80 (−)
14	 (**18**)	86	44 (+)
15	 (**19**)	59	34 (−)

[a] All reactions were carried out at 25 °C under 2.5 bar hydrogen for 24 h with 0.0012 mmol $[Rh(cod)_2]BF_4$, 0.0012 mmol bidentate ligand or 0.0024 mmol monodenate ligand, and 0.12 mmol **4** in dichloromethane (2.0 mL). Conversions and *ee* values were determined by GC (Optima 5 Amin, 50-8-260/5-8-280/5-8-300/10) and HPLC (Chiracel OJ, t_R = 37.5 ((+)-**4a**), 46.9 min ((−)-**4a**) (*n*-hexane/ethanol = 95:5, flow = 1.0 mL min^{-1})), respectively. bdpp = 2,4-bis(diphenylphosphanyl)pentane, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, bppm = 2,3-bis(diphenylphospanyl)-*N*-phenylmaleimide, ChiraPhos = 2,3-bis(diphenylphosphanyl)butane, DeguPhos = 3,4-bis(diphenylphosphino)-1-benzylpyrrolidine, diop = 2,2-dimethyl-4,5-bis(diphenylphosphanylmethyl)-1,3-dioxolane, DuPhos = 1,2-bis(phospholano)benzene, FerroTane = 1,1′-bis(2,4-diethylphos-photano)ferrocene, JosiPhos = 1-[2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine, MonoPhos = (3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)dimethylamine, PyrPhos = 3,4-bis(diphenylphosphanyl)pyrrolidine, Tol = *p*-tolyl.

Table 2. Hydrogenation of enamide **4** with various phospholane-based ligands.[a]



4 **4a**

Entry	Ligand	Conv. [%]	*ee* [%]
1	 (**16**)	>99	96 (−)
2	 (**20**)	93	97 (−)
3	 (**21**)	98	96 (−)
4	 (**22**)	99	96 (−)
5	 (**23**)	66	86 (−)
6	 (**24**)	95	68 (−)
7	 (**25**)	34	10 (−)

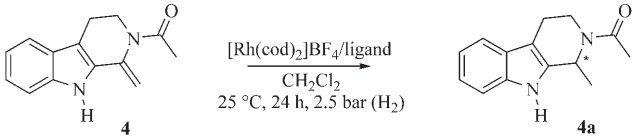
[a] All reactions were carried out at 25 °C under 2.5 bar hydrogen for 24 h with 0.0012 mmol $[Rh(cod)_2]BF_4$, 0.0012 mmol bidentate ligand or 0.0024 mmol monodenate ligand, and 0.12 mmol **4** in dichloromethane (2.0 mL). Conversions and *ee* values were determined by GC (Optima 5 Amin, 50-8-260/5-8-280/5-8-300/10) and HPLC (Chiracel OJ, t_R = 37.5 ((+)-**4a**), 46.9 min ((−)-**4a**) (*n*-hexane/ethanol = 95:5, flow = 1.0 mL min^{-1})), respectively. Cy = cyclohexyl.

and further ring expansion showed no improvement in enantioselectivity (Table 2, entries 3 and 4). A slight positive influence was found by changing the phthalimide ring to phthalate (Table 2, entry 2), whereas the acenaphthylene (**23**) and 2,5-dimethylthiophene backbones (**24** and **25**) gave lower enantioselectivity (Table 2, entries 5–7).[20]

Next, we investigated the influence of solvents and different hydrogen pressures on enantioselectivity and conversion with ligand **20** (Table 3). A crucial effect was noticed when the reaction was carried out in different solvents such as methylene chloride, toluene, ethyl acetate, THF, methanol, ethanol, and 2-propanol (Table 3, entries 2 and 6–11). The best enantioselectivity of up to 99 % *ee* was achieved by using ethyl acetate as solvent (Table 3, entry 7).

Generally, protic solvents triggered full conversion and lower enantioselectivity, in contrast to nonprotic solvents. In the case of toluene and THF, the diminished yield was probably caused by deactivation of the catalyst due to solvent coordination (Table 3, entries 2 and 6–11).[21] Increasing the hydrogen pressure above 10 bar yielded a negative effect on the enantioselectivity and conversion (Table 3, entries 1–5). A comparison of the behavior of the catalyst precursor prepared in situ and isolated showed no significant difference under standard conditions (Table 3, entries 1 and 2).

Table 3. Pressure and solvent dependency of the asymmetric hydrogenation of enamide **4** with [Rh(cod)(**20**)]BF_4.[a]



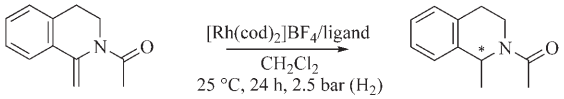
4 **4a**

Entry	Solvent	*P* [bar]	Conv. [%]	*ee* [%]
1[b]	CH_2Cl_2	2.5	93	97 (−)
2	CH_2Cl_2	2.5	95	97 (−)
3	CH_2Cl_2	10	>99	88 (−)
4	CH_2Cl_2	25	90	80 (−)
5	CH_2Cl_2	50	68	60 (−)
6	toluene	2.5	38	96 (−)
7	EtOAc	2.5	96	99 (−)
8	THF	2.5	25	32 (−)
9	MeOH	2.5	99	84 (−)
10	EtOH	2.5	99	74 (−)
11	2-PrOH	2.5	99	86 (−)

[a] All reactions were carried out at 25 °C under the corresponding pressure for 24 h with 0.0012 mmol [Rh(cod)(**20**)]BF_4 and 0.12 mmol **4** in 2.0 mL solvent. Conversions and *ee* values were determined by GC (Optima 5 Amin, 50-8-260/5-8-280/5-8-300/10) and HPLC (Chiracel OJ, t_R = 37.5 ((+)-**4a**), 46.9 min ((−)-**4a**) (*n*-hexane/ethanol = 95:5, flow = 1.0 mL min^{-1})), respectively. [b] Catalyst generated in situ containing 0.0012 mmol $[Rh(cod)_2]BF_4$ and 0.0012 mmol ligand **20**.

Applying similar reaction conditions to those described in Table 2, we hydrogenated **29** by using several rhodium diphosphane catalysts based on chiral phospholanes (Table 4).

Table 4. Hydrogenation of isoquinoline substrate **29**.[a]



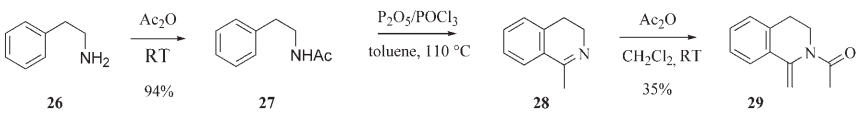
29 **29a**

Entry	Ligand	Conv. [%]	*ee* [%]
1	**16**	99 (>99)	96 (−) (82)[b]
2[c]	**20**	99	92 (−)
3	**21**	>99	94 (−)
4	**22**	98	88 (−)
5	**23**	99	84 (−)
6	**24**	99	50 (−)
7	**25**	99	58 (−)

[a] All reactions were carried out at 25 °C under 2.5 bar hydrogen for 24 h with 0.0012 mmol $[Rh(cod)_2]BF_4$, 0.0012 mmol bidentate ligand, and 0.12 mmol **29** in ethyl acetate (2.0 mL). Conversions and *ee* values were determined by GC and HPLC (ChiralPak-AD-H, t_R = 11.0 ((−)-**29a**), 13.7 min ((+)-**29a**) (*n*-heptane/ethanol = 95:5, flow = 1.0 mL min^{-1})), respectively. [b] The value in parentheses was obtained from an experiment performed in ethyl acetate. [c] Isolated complex [Rh(cod)(**20**)]BF_4.

While studying the effect of NH protection (Boc and Me; Boc = *tert*-butoxycarbonyl) on enantioselectivity and reaction rate, we observed inactivity of [Rh(cod)(**20**)]BF_4 under standard conditions. However, when the Ph-Binepine (**18**)-based rhodium catalyst was used in the hydrogenation of the Boc-protected substrate, enantioselectivities and yields of up to 78% and 33% *ee*, respectively, were achieved. Furthermore, we synthesized an enamide, based on substrate **4**, with a trisubstituted C=C double-bond motif. Unfortunately, no conversion was observed at all in the asymmetric hydrogenation with the complex [Rh(cod)(**20**)]BF_4 when a benzyl group was present.[22]

Next, we investigated the asymmetric reduction of the related isoquinoline precursor **29** (Scheme 3). Recently, Hashimoto, Saigo, and co-workers reported the asymmetric hydrogenation of substrate **29** with a rhodium diphosphane catalyst.[10h] Enantioselectivities of up to 85% *ee* were obtained under optimized conditions.[10e] Enamide **29** was synthesized according to the described procedure (see below) by acylation of 2-phenylethylamine (**26**) with neat acetic anhydride, subsequent ring formation by Bischler–Napieralski reaction in the presence of P_2O_5, and finally double-bond shift to the exocyclic position by acetylation of imine **28** with acetic anhydride (Scheme 3).[23]



26 **27** **28** **29**

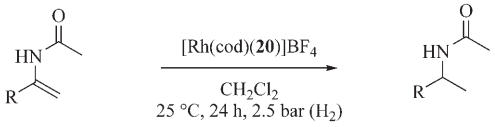
Scheme 3. Synthesis of isoquinoline substrate **29**.

Excellent enantioselectivities and yields were achieved in the presence of phthalimide- and phthalate-based ligand backbones (Table 4, entries 1–3). Notably, higher enantioselectivity was attained with dichloromethane instead of ethyl acetate as solvent (Table 3, entry 1). The best enantioselectivity (96% *ee*) was achieved with the system containing ligand **16**. When the acenaphthylene and 2,5-dimethylthiophene backbones were used, we found an indication that two chiral phospholane units were beneficial for obtaining good enantioselectivities (Table 4, entries 5–7).

On the basis of these encouraging results, we tested the catalyst in the reduction of other enamides. Table 5 summarizes the conversions and enantioselectivities attained in the hydrogenation of the simple enamides **30**–**36** with the commercially available preformed Rh complex of ligand **20**. In the case of aryl enamides **30**–**34**, the obtained conversions were excellent, and the *ee* values are comparable to those for substrates **4** and **29**, which confirms the ability of the catalyst to hydrogenate various enamides with high activity and good to excellent enantioselectivity.

Electron-donating substituents on the phenyl ring did not improve the enantioselectivity (Table 5, entries 2–4), but the catalyst appeared to be tolerant towards *ortho* substitution, with only a slight decrease in enantiomeric excess. Electron-withdrawing substituents, on the other hand, slightly enhanced the enantioselection (Table 5, entry 5). In a similar manner to substrate **4**, ligand **20** turned out to be more selective (90% *ee*) with ethyl acetate as solvent (Table 5, entry 1). Notably, the bulky *tert*-butylaceto-

Table 5. Asymmetric hydrogenation of substituted *N*-(1-arylvinyl)acetamides **30**–**34** and acetoenamides **35** and **36**.[a]



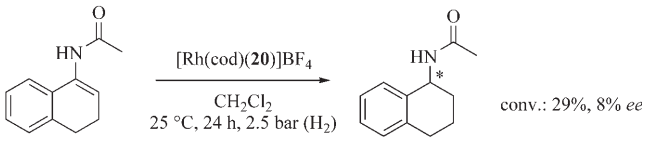
30-36 **30a-36a**

Entry	Enamide	R	Conv. [%][b]	*ee* [%][b,c]
1	**30**	C_6H_5	99	86 (*R*) (90)[d]
2	**31**	*p*-CH_3O-C_6H_4	>99	84 (*R*)
3	**32**	*m*-CH_3O-C_6H_4	>99	85 (*R*)
4	**33**	*o*-CH_3O-C_6H_4	99	80 (*R*)
5	**34**	*p*-CF_3-C_6H_4	>99	89 (*R*)
6	**35**	*tert*-butyl	94	96 (+)
7	**36**	2-thiophene	>99	92 (+)

[a] All reactions were carried out at 25 °C under 2.5 bar hydrogen for 24 h with 0.0024 mmol [Rh(cod)(**20**)]BF_4 and 0.24 mmol substrate in 2.0 mL CH_2Cl_2. [b] Conversion of enamides **30**–**34** was determined by GC (Agilent Technologies, 30 m, 50–300 °C), *ee* values were determined by HPLC (ChiralPak AD-H): t_R = 6.6 ((*R*)-**30a**), 8.8 ((*S*)-**30a**) (*n*-heptane/ethanol = 95:5, flow = 1.0 mL min^{-1}), 20.3 ((*R*)-**31a**), 29.5 ((*S*)-**31a**) (*n*-heptane/ethanol = 98:2, flow = 1.5 mL min^{-1}), 30.6 ((*R*)-**32a**), 33.6 ((*S*)-**32a**), 11.4 ((*R*)-**33a**), 17.3 ((*S*)-**33a**) (*n*-heptane/ethanol = 95:5, flow = 1.0 mL min^{-1}), 12.7 ((*S*)-**34a**), 16.9 min ((*R*)-**34a**) (*n*-heptane/ethanol = 95:5, flow = 0.8 mL min^{-1}); conversion and *ee* of **35** were determined by GC (Lipodex E, 25 m): t_R = 49.0 ((+)-**35a**), 50.4 min ((−)-**5a**); conversion and *ee* of **36** were determined by GC (Optima) and HPLC (Chiralcel OD-H, heptane/ethanol = 98:2, flow = 1.0 mL min^{-1}), respectively: t_R = 27.0 ((−)-**36a**), 32.4 min ((+)-**36a**). [c] The absolute configuration of the product was assigned by analogy. [d] The value in parenthesis was obtained from an experiment performed in ethyl acetate.

enamide and the heterocyclic 2-thiophenylacetoenamide are easy to hydrogenate with this catalyst, and excellent optical purity of **35a** and **36a** were obtained (Table 5, entries 6 and 7).

Next, the more challenging endocyclic enamide **37** was synthesized. The substrate with an internal double bond was much less reactive to hydrogenation under these conditions, and very low *ee* was observed, probably due to shielding of the double bond (Scheme 4).



37 **37a**

Scheme 4. Reduction of endocyclic substrate **37**. Conversion was determined by GC (Agilent Technologies, 30 m, 50–300 °C; t_R = 20.7 (**37**), 19.7 min (**37a**)), *ee* values were determined by HPLC (Chiralpak AD-H, heptane/ethanol = 95:5, flow = 1 mL min^{-1}).

Conclusions

We have demonstrated the usefulness of asymmetric hydrogenation for the synthesis of optically active tetrahydro-β-carbolines by using rhodium catalysts. Enantioselectivities of up to 99% *ee* with cat*A*Sium M ligands were obtained after ligand screening and optimization of the reaction conditions. The scope and limitation of the rhodium catalysts containing cat*A*Sium M ligands have been shown in the reduction of dihydroisoquinoline and other benchmark enamides with excellent enantioselectivities.

Experimental Section

General

All manipulations were performed under argon atmosphere with standard Schlenk techniques. Toluene was distilled from sodium benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Ethanol and 2-propanol were distilled from Na under argon. Methylene chloride was distilled from CaH_2 under argon. Ethyl acetate (on molecular sieves) was purchased from Fluka and was used without further purification. [Rh(cod)$_2$]BF_4 (purchased from Fluka) was used without further purification.

Syntheses

2: Method A:[24] Triethylamine (30.8 mmol) and a solution of the acetyl chloride (28.4 mmol) in dichloromethane (10 mL) were added carefully to a suspension of the tryptamine (28 mmol) in dichloromethane (30 mL) under an atmosphere of argon at room temperature. After the mixture was heated under reflux for 3 h, the solution was washed with aqueous HCl and brine and dried over $MgSO_4$. The solvent was removed under vacuum, and an oily residue was obtained, which was dissolved in small amounts of dichloromethane. Subsequent addition of *n*-hexane yielded crystals of *N*-(2-(1*H*-indol-3-yl)ethyl)acetamide (**2**). Method B: A solution of tryptamine (99 mmol) in acetic anhydride (50 mL) was stirred for 48 h at room temperature. After addition of water/ice, the aqueous solution was extracted three times with diethyl ether (100 mL). The organic layer was neutralized with aqueous $NaHCO_3$, dried over Na_2SO_4, and reduced under vacuum to obtain an oil, which was dissolved in a small amount of dichloromethane. Subsequent addition of *n*-hexane yielded crystals of **2**. Yield: 81% (method A); 94% (method B) (yellow crystals crystallized from dichloromethane/*n*-hexane). R_f = 0.42 (CH_2Cl_2/MeOH = 95:5); m.p.: 80–82 °C; IR (KBr): $\tilde{\nu}$ = 3400 (s), 3259 (s), 3084 (m), 2968 (m), 2940 (m), 2895 (m), 2850 (m), 1929 (w), 1893 (w), 1774 (w), 1633 (s), 1564 (m), 1458 (m), 1435 (m), 1373 (m), 1337 (m), 1298 (m), 1276 (m), 1246 (w), 1224 (m), 1209 (m), 1126 (w), 1094 (m), 1064 (m), 1012 (m), 987 (w), 929 (w), 877 (w), 845 (w), 800 (m), 745 (s), 610 (m), 579 (m), 560 (w), 487 (m), 461 (m), 421 cm^{-1} (m); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (br, 1H, NH), 7.62–7.60 (m, 1H), 7.40–7.37 (m, 1H), 7.25–7.11 (m, 2H), 7.03 (d, J = 2.26 Hz, 1H), 5.61 (br, 1H, NH), 3.60 (q, J = 6.43 Hz, 2H), 2.98 (dt, J = 6.72, 0.75 Hz, 2H), 1.93 ppm (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.2, 136.2, 127.1, 122.7, 121.9, 121.8, 119.2, 118.4, 111.1, 39.6, 25.0, 23.1 ppm; MS (ESI): *m/z* (%) = 202 $[M]^+$ (32), 143 (100), 105 (8), 130 (99), 121 (10), 115 (13), 103 (14), 77 (16), 69 (22); HRMS: *m/z* calcd for $C_{12}H_{14}ON_2$: 202.11006; found: 202.109792.

3: Phosphorus oxychloride (60 mmol) and phosphorus pentoxide (60 mmol) were added carefully to a suspension of **2** (15.3 mmol) in toluene (100 mL). The solution was stirred for 1 h at 110 °C. After the mixture was cooled to room temperature, the solvent was removed, and the residue was washed with diethyl ether (2 × 50 mL), carefully treated with water and aqueous HCl, and heated to 90 °C, then water was added until a clear solution was formed. The solution was extracted with diethyl ether (100 mL), and the aqueous layer was treated with sodium hydroxide until pH ≈ 12. After extraction with diethyl ether (5 × 100 mL), the organic layer was dried over Na_2SO_4, and removal of the solvent yielded orange crystals, which were purified by sublimation in vacuum and/or crystallization to afford 1-methyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (**3**). Yield: 48% (off-white crystals crystallized from acetonitrile). M.p.: 175–176 °C; IR (KBr): $\tilde{\nu}$ = 3420 (m), 3136 (m), 3104 (m), 3073 (m), 3032 (m), 2989 (m), 2938 (s), 2880 (m), 2840 (m), 2770 (m), 2664 (w), 1724 (w), 1623 (m), 1606 (m), 1575 (m), 1551 (s), 1506 (m), 1471 (m), 1446 (m), 1427 (m), 1376 (m), 1325 (s), 1307 (m), 1278 (m), 1250 (m), 1222 (m),

1171 (w), 1149 (w), 1123 (w), 1074 (w), 1018 (w), 1006 (w), 983 (w), 917 (w), 983 (m), 917 (w), 903 (w), 870 (w), 812 (w), 736 (s), 726 (m), 652 (w), 621 (w), 575 (w), 562 (w), 534 (w), 493 (w), 433 cm^{-1} (w); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.66$ (br, 1H, NH), 7.55–7.52 (m, 1H), 7.34–7.31 (m, 1H), 7.23–7.17 (m, 1H), 7.11–7.05 (m, 1H), 3.83 (dt, $J = 8.43$, 1.56 Hz, 2H), 2.80 (t, $J = 8.51$ Hz, 2H), 2.30 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 157.6$, 136.3, 128.9, 125.3, 124.2, 120.1, 119.8, 116.3, 111.7, 48.1, 21.9, 19.2 ppm; MS (ESI): m/z (%) = 183 $[M]^+$ (100), 171 (8), 154 (14), 143 (8), 128 (8), 115 (8), 77 (6), HRMS: m/z calcd for $C_{12}H_{11}N_2$: 183.09167; found: 183.091744.

4: A solution of **3** (19.9 mmol) and acetic anhydride (53 mmol) in dichloromethane (40 mL) was stirred for 12 h at room temperature. The solution was poured onto ice (100 g) and made basic with $KHCO_3$. The aqueous layer was extracted with dichloromethane (2×100 mL). The organic layer was dried over Na_2SO_4, and removal of the solvent yielded a brown residue, which was purified by crystallization to afford 1-(1-methylene-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)ethanone (**4**). Yield: 82% (orange crystals crystallized from acetonitrile). M.p.: 225–227 °C (decomp.); IR (KBr): $\tilde{\nu} = 3293$ (s), 3117 (w), 3083 (w), 3009 (w), 2918 (w), 2894 (w), 2839 (w), 1929 (w), 1889 (w), 1767 (w), 1741 (w), 1618 (s), 1543 (m), 1501 (m), 1475 (m), 1454 (m), 1443 (m), 1400 (s), 1378 (s), 1359 (m), 1325 (m), 1302 (m), 1271 (m), 1248 (m), 1233 (s), 1206 (m), 1188 (m), 1157 (m), 1131 (m), 1113 (m), 1067 (m), 1035 (m), 1009 (m), 989 (m), 943 (m), 894 (m), 865 (s), 760 (m), 738 (s), 713 (m), 701 (m), 670 (m), 643 (m), 621 (m), 604 (m), 579 (m), 560 (w), 535 (w), 510 (m), 470 (m), 438 (m), 423 cm^{-1} (m); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (br, 1H, NH), 7.52–7.47 (m, 1H), 7.36–7.30 (m, 1H), 7.25–7.18 (m, 1H), 7.14–7.07 (m, 1H), 5.35 (d, $J = 1.32$ Hz, 1H, $=CH_2$), 4.99 (br, 1H, $=CH_2$), 4.13 (t, $J = 5.75$ Hz, 2H), 2.87 (t, $J = 5.75$ Hz, 2H), 2.29 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 170.3$, 136.9, 129.6, 126.8, 123.8, 120.1, 119.2, 111.1, 101.7, 43.3, 23.0, 21.5 ppm; MS (ESI): m/z (%) = 226 $[M]^+$ (95), 183 (100), 155 (35), 128 (9); HRMS: m/z calcd for $C_{14}H_{14}NO$: 226.11006; found: 226.110131.

29: Phosphorus pentoxide (0.35 mol) was added carefully in several portions to a suspension of *N*-phenethylacetamide (92 mmol) in xylene (200 mL). The solution was stirred for 2 h at 110 °C. After the mixture was cooled to room temperature, the solvent was removed, and the residue was washed with diethyl ether (50 mL), carefully treated with water and aqueous HCl, and heated to 90 °C, then water was added until a clear solution was formed. The solution was extracted with diethyl ether (100 mL), and the aqueous layer was treated with sodium hydroxide until pH ≈ 12. After extraction with diethyl ether (4×100 mL), the organic layer was dried over Na_2SO_4, and removal of the solvent yielded an oily residue. The residue was treated with a solution of acetic anhydride (0.25 mmol) in dichloromethane (50 mL), and the mixture was stirred for 12 h at room temperature. The solution was poured onto ice and made basic with $KHCO_3$. The aqueous layer was extracted with dichloromethane (2×200 mL). The organic layer was dried over Na_2SO_4, and removal of the solvent yielded a brown residue, which was purified by flash chromatography (CH_2Cl_2/methanol = 99:1). The yellow oil obtained was dissolved in petroleum ether, and colorless crystals of 1-(1-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone (**29**) were formed at −30 °C. Yield: 35%. M.p.: 65–68 °C; IR (ATR): $\tilde{\nu} = 3257$ (w), 3111 (w), 3057 (w), 3013 (w), 3000 (w), 2942 (w), 2929 (w), 2833 (w), 1942 (w), 1810 (w), 1628 (s), 1598 (m), 1487 (w), 1453 (m), 1426 (m), 1391 (s), 1364 (s), 1306 (m), 1259 (m), 1259 (m), 1234 (m), 1203 (m), 1153 (m), 1114 (m), 1093 (m), 1039 (m), 1011 (w), 997 (m), 958 (w), 937 (w), 898 (s), 866 (w), 826 (m), 775 (s), 747 (s), 719 (m), 682 cm^{-1} (m); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$–7.62 (m, 1H), 7.30–7.12 (m, 3H), 5.76 (d, $J = 0.87$ Hz, 1H, $=CH_2$), 5.06 (br, 1H, $=CH_2$), 3.99 (t, $J = 6.12$ Hz, 2H, CH_2), 2.92 (t, $J = 6.09$ Hz, 2H, CH_2), 2.23 ppm (s, 3H, $C(O)CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.3$, 134.9, 131.5, 129.2, 128.7, 126.4, 124.0, 106.2, 71.8 41.4, 28.8, 22.4 ppm; MS (ESI): m/z (%) = 187 $[M]^+$ (42), 144 (100), 115 (38); HRMS: m/z calcd for $C_{12}H_{13}NO$: 187.09917; found: 187.099164.

General procedure for the synthesis of **30**–**35**: A solution of the corresponding benzonitrile (17.0 mmol) in diethyl ether (20 mL) was added dropwise to a stirred solution of methyl magnesium bromide (17.0 mmol, 3.0 mol L^{-1} in diethyl ether, 6.0 mL) in diethyl ether (50 mL) at 0 °C over a period of 30 min. After complete addition, the solution was heated under reflux for 8 h. Within a few hours, a yellow precipitate was formed. The reaction mixture was then cooled to 0 °C, and a solution of acetic anhydride (17.0 mmol) in diethyl ether (20 mL) was added carefully over 30 min. The reaction mixture was heated under reflux for 8 h. Methanol was added with stirring to the resulting suspension at room temperature until all precipitates were dissolved (≈50 mL). The homogeneous solution was mixed with water/ethyl acetate (1:1, 100 mL). After phase separation, the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic layers were dried with $MgSO_4$. After the solvents were removed, the semicrystalline crude oil was purified by column chromatography (*n*-hexane/ethyl acetate = 1:1). Removal of the solvent yielded the crystalline products. The analytical data are in agreement with those reported in the literature.[12i]

General procedure for the synthesis of **36**: A stirred solution of the corresponding ketone (30.3 mmol), hydroxylamine hydrochloride (73 mmol), and pyridine (62.2 mmol) in ethanol (40 mL) was heated to 85 °C for 16 h. The solvent was removed, and the residue was dissolved in ethyl acetate/water. The organic phase was washed two times with water (20 mL) and dried with $MgSO_4$. After removal of the solvents, the product was recrystallized from toluene. The corresponding ketoximine (18.6 mmol) was dissolved in toluene (30 mL) under argon. Acetic acid anhydride (55.9 mmol), acetic acid (55.9 mmol), and Fe powder (37.3 mmol, Aldrich 325 mesh) were added to the stirred solution, which was then heated to 70 °C for 4 h. The mixture was filtered through a plug of celite after being cooled to room temperature. Dichloromethane was added to the filtrate, followed by washing with 2.0 M NaOH (2×25 mL) at 0 °C. The separated organic phase was concentrated to half volume. The crystalline product was obtained after 12 h at 0 °C. The crystals were filtered and dried under vacuum. The analytical data are in agreement with those reported in the literature.[12f,25]

General procedure for the catalytic hydrogenation of enamides: A solution of enamide (0.12 or 0.24 mmol) in solvent (1.0 mL) was transferred by syringe into an autoclave. The catalyst was generated in situ by mixing $[Rh(cod)_2]BF_4$ (0.0012 or 0.0024 mmol) and the corresponding ligand (0.0012 or 0.0024 mmol; 0.0024 mmol for monodentate ligands) in solvent (1.0 mL) for 10 min, after which the mixture was transferred by syringe into the autoclave. Next, the autoclave was charged with hydrogen, and the mixture was stirred at the required temperature. After the predetermined time, the hydrogen was released, and the reaction mixture was passed through a short plug of silica gel. The enantioselectivity and conversion were measured by GC or HPLC without further modifications.

4a: 1-(1-Methyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)ethanone: White crystals crystallized from ethyl acetate after purification by flash column chromatography (ethyl acetate/*n*-hexane = 10:1). $R_f = 0.2$ (ethyl acetate/*n*-hexane = 10:1); m.p.: 198–200 °C; IR (KBr): $\tilde{\nu} = 3402$ (m), 3189 (s), 3116 (m), 3085 (m), 2971 (m), 2919 (w), 2872 (w), 2740 (w), 1735 (w), 1611 (s), 1592 (m), 1499 (w), 1474 (m), 1452 (s), 1370 (m), 1325 (m), 1305 (m), 1280 (w), 1243 (m), 1179 (m), 1163 (m), 1147 (w), 1093 (w), 1066 (w), 1052 (w), 1027 (m), 1008 (w), 970 (m), 922 (w), 905 (w), 883 (w), 843 (w), 764 (m), 744 (m), 736 (m), 704 (w), 611 (m), 596 (m), 503 (w), 468 (w), 427 cm^{-1} (w); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.31$ (br, 1H, NH), 7.45–7.50 (m, 1H, 12-H or 9-H), 7.32–7.37 (m, 1H, 12-H or 9-H), 7.07–7.23 (m, 2H, 10-H and 11-H), 5.81 (q, $J = 6.75$ Hz, 1H, CH_3CH), 3.98–4.06 (m, 1H, CH_2), 3.45–3.56 (m, 1H, CH_2), 2.82–2.87 (m, 2H, CH_2), 2.25 (s, 3H, $C(O)CH_3$), 1.49 ppm (d, $J = 6.75$ Hz, 3H, $CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.2$, 136.1, 135.2, 126.6, 121.7, 119.5, 117.9, 111.0, 107.2, 45.1, 40.8, 22.1, 22.0, 19.1 ppm; MS (ESI): m/z (%) = 228 $[M]^+$ (77), 213 (51), 185 (19), 171 (100), 156 (24), 144 (15), 128 (10), 115 (11), 43 (11); HRMS: m/z calcd for $C_{14}H_{16}ON_2$: 228.12571; found: 228.125660.

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