Asymmetric Synthesis of 3-Substituted Dihydro-2*H*-isoquinolin-1-ones, Dihydro- and Tetrahydroisoquinolines via 1,2-Addition/Ring Closure

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Abstract: The asymmetric synthesis of 3-substituted dihydro-2*H*-isoquinolin-1-ones, dihydro- and tetrahydroisoquinolines is described. The key operation is a tandem 1,2-addition/ring closure sequence employing lithiated *ortho*-toluamides and aldehyde SAMP- or RAMP-hydrazones as substrates, followed by N–N bond cleavage to remove the auxiliary. Moderate to good yields and high enantiomeric excesses (ee = 85–99%) are reached.

Key words: asymmetric synthesis, nucleophilic addition, cyclisation, hydrazones, heterocycles

The stereoselective synthesis of compounds containing a tetrahydroisoquinoline skeleton is a field of growing interest in synthetic organic chemistry as these compounds display a unique structure and a broad spectrum of biological properties.[1] For instance, ecteinascidin 743 (Et 743) belonging to the saframycin family shows strong antitumor activity and is currently in phase II of clinical trials.[2] Another representative example (+)-tetrahydropalmatine, is an analgesic, sedative and hypnotic agent[3] and belongs to the protoberberine family, a large class of naturally occurring alkaloids possessing antitumor, antimicrobial and other biological activities.[4d,e,5] The asymmetric synthesis of 1-substituted tetrahydroisoquinolines has been developed to a large extent[6,7] as they are part of many naturally occurring alkaloids.[1] In contrast, the stereoselective synthesis of 3-substituted tetrahydroisoquinolines or tetrahydroisoquinolinones has less precedent in the literature.[7,8] Especially, 3-aryl tetrahydroisoquinolines are of considerable interest as synthetic intermediates for the elaboration of related alkaloids like protoberberines, pavines or benzo[*c*]phenanthridines.[1,4]

An important entry to the title isoquinoline heterocycles is the general concept of nucleophilic addition/cyclization first outlined by McLean et al., who obtained 13-hydroxy-8-oxoprotoberberines from lithiated phthalide anions and 3,4-dihydroisoquinolines.[9] In a related approach, Clark et al. pioneered a non-stereoselective tandem addition/cyclization of lithiated 2-methyl-benzamides with imines to yield 3-substituted dihydro-2*H*-isoquinolin-1-ones with low to moderate yields.[10] Since then, the lateral metalation methodology[11] has been applied stereoselectively in moderate yields using enantiopure imines,[12] or in low yields and good enantioselectivity using racemic imines and (–)-sparteine.[5b] Good overall yields and high enantioselectivities were obtained in a three-step process using chiral sulfinimines.[5c,e] Later, these two concepts were combined and 8-oxoprotoberberines were assembled upon condensation of *ortho*-toluamides incorporating chiral auxiliaries with 3,4-dihydroisoquinoline in moderate yields and high enantiomeric excesses.[13] (–)-Sparteine has also been used instead of an auxiliary giving moderate yield and low to good enantioselectivity.[14]

Recently, we reported on the first asymmetric synthesis of 3-aryl-substituted 2,3-dihydro-1*H*-isoindol-1-ones by 1,2-addition of *ortho*-lithiated benzamides to aldehyde SAMP/RAMP hydrazones.[15] We now wish to disclose an asymmetric synthesis of the title isoquinoline heterocycles **4**, **5** and **6** by nucleophilic 1,2-addition of lithiated *N*,*N*-diethyl-2-methylbenzamides **1** to aldehyde SAMP- or RAMP-hydrazones **2** and subsequent removal of the auxiliary from the resulting 3,4-dihydro-2*H*-isoquinolin-1-one derivatives **3** by N–N bond cleavage (Scheme 1).

A first approach to synthesize *N*-amino-substituted 3-phenyl-3,4-dihydro-2*H*-isoquinolin-1-one **3a** employed 3.5 equivalents of lithiated *N*,*N*-diethyl-2-methylbenzamide **1a** and addition to benzaldehyde-SAMP-hydrazone **2a**. A

Table 1 Synthesis of (*2S,3R*)-**3a** from **1a**, Optimization of Conditions

Entry	**1a** (equiv)	Metalation Temp (°C)	Additive	Addition Temp (°C)	Yield of (2*S*,3*R*)-**3a** (%)
1	3.5	–78	–	–78 to r.t.	37
2	10	–78	–	–78 to r.t.	46
3	5	–78	$BF_3{\cdot}OEt_2$	–78 to r.t.	21
4	5	–78	LiCl	–78 to r.t.	43
5	5	–78	LiI	–78 to r.t.	31
6	7	–40	–	–40	52[a]
7	7	–78	$Yb(OTf)_3$	–40	50
8	**7**	**–40**	**$AlMe_3$**	**–40**	**70**
9	7	–78	$AlMe_3$	–20	45
10	7	–78	$AlMe_3$	–60 to –78	25

[a] With RAMP as auxiliary.

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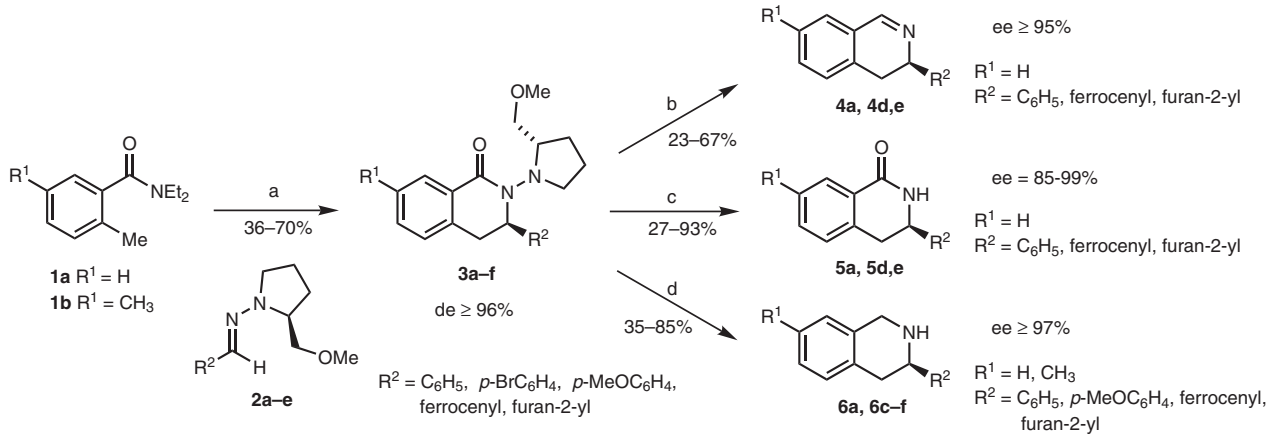

Scheme 1 *Reagents and conditions*: (a) LDA, THF, –40 °C then **2a–e**, $AlMe_3$, THF, –40 °C, 16–18 h; (b) Li or Ca, NH_3 (l), THF, reflux, 5 min; (c) 1) acetyl chloride, MeOH; 2) Zn, AcOH, 6 N HCl,))), 15 min then reflux, 36 h (method A) or MMPP·$6H_2O$, MeOH, r.t., 24–96 h (method B) or SmI_2, THF, r.t., 30 min (method C); (d) 1) excess BH_3·THF, THF, reflux, 4 h; 2) 1 N HCl, reflux, 1 min.

yield of 37% of **3a** was obtained (Table 1, entry 1). The open-chain product resulting from a single 1,2-addition reaction could not be detected, indicating that the reaction took place in a tandem 1,2-addition ring closure process. As shown in Table 1, the reaction conditions were optimized varying the number of equivalents of **1a**, the temperature of metalation and addition and the additive. A large excess of lithiated *ortho*-toluamide **1a** slightly improved the yield (entry 1 vs. 2). Various additives like BF_3·OEt_2, LiCl, LiI and $Yb(OTf)_3$ were examined, but none of them was found to have a significant effect on the reaction (entries 3 to 5, entry 7). When the metalation and the addition were conducted at a temperature of –40 °C, the yield could be increased to 52% (entry 6 vs. 2). Referring to the positive effects trimethylaluminum had on the nucleophilic 1,2-addition of organolithiums to enantiomerically pure *N*-sulfinyl ketimines,[16] this Lewis acid was then envisaged. Its presence resulted in the best yield so far (70%, entry 8). Higher (entry 9) and lower reaction temperatures (entry 10) did not result in any further improvements.

Consequently, 3,4-dihydro-2*H*-isoquinolin-1-ones **3a–e** were then synthesized under the optimized conditions employing the aromatic aldehyde SAMP- or RAMP-hydrazones **2a–e**[15,17] (Scheme 1, Table 2). To a further extend the scope of the reaction was attempted by substitution at the aromatic ring of the *N*,*N*-diethylbenzamide **1**. Indeed *N*,*N*-diethyl-2,5-dimethylbenzamide **1b** was employed successfully with the ferrocenyl aldehyde hydrazone **2d** (entry 7 and 8). It is assumed that the lower yield could be due to competitive deprotonation of the *meta*-methyl group and addition to the SAMP-hydrazone (entries 7 and 8 vs. 4). Interestingly, the formation of **3e** and **3f** was found to give better results without trimethylaluminium (entry 5 vs. 6, entry 7 vs. 8).

Methods for the N–N bond cleavage of the auxiliary were then investigated. We initially examined to use lithium in

Table 2 Tandem 1,2-Addition/Ring Closure of Lithiated *N*,*N*-Diethyl-2-methylbenzamides **1a**,**b** with Aldehyde SAMP- or RAMP-Hydrazones **2a–e** to Afford 3- and *N*-Substituted 3,4-Dihydro-2*H*-isoquinolin-1-ones **3a–f**

Entry	**1**	R^1	**2**	R^2	Additive	**3**	Yield (%)	de[a] (%)
1	**1a**	H	(*S*)-**2a**	Phenyl	$AlMe_3$	(2*S*, 3*R*)-**3a**	70	≥96
2	**1a**	H	(*S*)-**2b**	*p*-Bromphenyl	$AlMe_3$	(2*S*, 3*R*)-**3b**	65	≥96
3	**1a**	H	(*S*)-**2c**	*p*-Methoxyphenyl	$AlMe_3$	(2*S*, 3*R*)-**3c**	39	≥96
4	**1a**	H	(*S*)-**2d**	Ferrocenyl	$AlMe_3$	(2*S*, 3*R*)-**3d**	63	≥96
5	**1a**	H	(*S*)-**2e**	Furan-2-yl	$AlMe_3$	(2*S*, 3*R*)-**3e**	40	≥96
6	**1a**	H	(*R*)-**2e**	Furan-2-yl	–	(2*R*, 3*S*)-**3e**	45	≥96
7	**1b**	CH_3	(*S*)-**2d**	Ferrocenyl	$AlMe_3$	(2*S*, 3*R*)-**3f**	36	≥96
8	**1b**	CH_3	(*R*)-**2d**	Ferrocenyl	–	(2*R*, 3*S*)-**3f**	46	≥96

[a] Determined by ^1H and ^{13}C NMR after column chromatography.

liquid ammonia as it had been previously employed to cleave hydrazines which have been activated by prior conversion to amide or carbamate derivatives.[18] Yet, when we applied these conditions to hydrazine (2*S*,3*R*)-**3a**, only traces of the expected 3,4-dihydro-2*H*-isoquinolin-1-one (*R*)-**5a** were obtained together with 44% of 3,4-dihydroisoquinoline (*R*)-**4a** in an excellent enantiomeric excess (ee ≥96%) (Scheme 1, Table 3, entry 1). This product is probably formed by reduction of the carbonyl group and subsequent dehydration. We were interested in developing the asymmetric synthesis of this unexpected product because it can be readily transformed into 1,3-disubstituted tetrahydroisoquinolines. Indeed, high 1,3-asymmetric inductions were reported by nucleophilic addition of allylic tin reagents to chiral 3-substituted 3,4-dihydroisoquinolines.[19] The enantioselective addition of organometallic compounds to 3,4-dihydroisoquinoline in the presence of oxazoline ligands is also known.[20] Addition of phthalide anions[9] or *ortho*-toluamide anions[13,14] to these chiral 3-substituted dihydroisoquinolines could be envisaged too, to give 6-substituted 8-oxoprotoberberines.

We then decided to use calcium as the reducing agent since it is considered to be less reactive than the alkali metals.[21] Yet, when calcium was employed, a predominant formation of **4a** (67%) was observed (Table 3, entry 2). Interestingly, replacement of lithium by calcium for the auxiliary cleavage of **3d** resulted in lower yields (Table 3, entry 3 vs. 4) in addition to the formation of considerable amounts of **5d** (44%, ee = 95%). In the same manner, **4e** (32%) was obtained using the calcium cleavage conditions (Table 3, entry 5).

In order to obtain 3-substituted 3,4-dihydro-2*H*-isoquinolin-1-ones **5**, another cleavage method using zinc in acetic acid was investigated (Scheme 1, step c, method A, Table 4) that had already been reported for N–N bond cleavage[22] and in particular for hydrazines derived from SAMP[23] or related hydrazones.[24] Using standard conditions only minor conversion of **3a** into the desired product **5a** could be observed, which led us to conclude that prior to any cleavage the N–N bond should be weakened first. Hence, the hydrazines **3a**, **3c** and **3e** were first reacted with a methanolic solution of hydrochloric acid. After concentration under reduced pressure, the resulting hydrochloride salts were dissolved in acetic acid and zinc powder was added. However, this method was found not to be very effective. The yield was moderate for **5a**, although displaying high enantioselectivity (Table 4, entry 1). Compound **5d** was obtained in 91% yield with complete racemization (Table 4, entry 4) and a low yield was obtained for **5e** together with racemization (Table 4, entry 6). We then investigated a second cleavage method using MMPP (Scheme 1, step c, method B, Table 4) as it has already been used successfully to cleave N–N bonds of hydrazines derived from SAMP[15,25] or related hydrazones.[26] This method was found to be partially effective as the yield of **5a** was good and no racemization was observed (Table 4, entry 2). With **3d**, a complex mixture of non-identified by-products was obtained (Table 4, entry 5). The yield of **5e** was very low, although the reaction took place without any racemization (Table 4, entry 7). We then opted for SmI_2 (Scheme 1, step c, method C, Table 4) as it has been reported to be efficient for hydrazines activated through a benzoyl function.[27] Compound **3a** was the only substrate subjected to these conditions, however, the result was very promising as the product was obtained in excellent yield and enantiomeric excess (Table 4, entry 3).

Table 4 Various N–N Cleavage Methods from 3-Subtituted 3,4-Dihydro-2*H*-isoquinolin-1-ones **5a**, **5d** and **5e**

Entry	**5**	R^2	Method	Yield (%)	ee[a] (%)
1	(*R*)-**5a**	Phenyl	A[b]	43	≥96
2	(*R*)-**5a**	Phenyl	B[c]	71	≥99
3	(*R*)-**5a**	Phenyl	C[d]	93	≥98
4	(*R*)-**5d**	Ferrocenyl	A[b]	91	0
5	(*R*)-**5d**	Ferrocenyl	B[c]	0	–
6	(*S*)-**5e**[e]	Furan-2-yl	A[b]	27	85
7	(*R*)-**5e**	Furan-2-yl	B[c]	14	99

[a] Determined by HPLC on a chiral stationary phase.
[b] Zinc in acetic acid.
[c] $MMPP{\cdot}6H_2O$.
[d] SmI_2.
[e] (2*R*,3*S*)-**3e** was used as starting material.

Table 3 N–N Cleavage with Lithium or Calcium in Liquid Ammonia to Form the 3-Substituted 3,4-Dihydroisoquinolines **4a**, **4d** and **4f**

Entry	**3**	R^2	Metal	**4**	Yield (%)	ee[a] (%)
1	(2*S*,3*R*)-**3a**	Phenyl	Li	(*R*)-**4a**	44	≥96
2	(2*R*,3*S*)-**3a**	Phenyl	Ca	(*S*)-**4a**	67	≥96
3	(2*S*,3*R*)-**3d**	Ferrocenyl	Li	(*R*)-**4d**	40	≥96
4	(2*R*,3*S*)-**3d**	Ferrocenyl	Ca	(*S*)-**4d**	23[b]	95
5	(2*R*,3*S*)-**3e**	Furan-2-yl	Ca	(*S*)-**4e**	32	n.d.

[a] Determined by ^1H NMR with (*R*)-(–)-anthr-9-yl-2,2,2-trifluoroethanol.
[b] 44% of (*S*)-**5d** (ee = 95%) was also formed.

Recrystallization of (*R*)-**5a** allowed us to perform an X-ray structure analysis (Figure 1).[28] The assignment of the absolute configuration of the new stereocenter was not possible, however, Davis et al. reported the asymmetric synthesis of (*S*)-**5a** ($[\alpha]_D^{20}$ = –203.4 (c = 1.03, $CHCl_3$)).[5e]

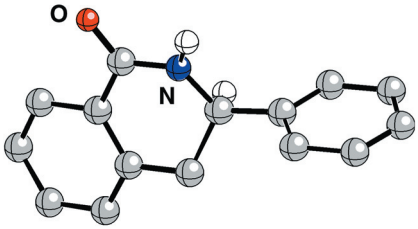

Figure 1 X-ray crystal structure of (*R*)-**5a**.[28]

By comparison with the optical rotation of (*R*)-**5a** ($[\alpha]_D^{23}$ = +195.3 (c = 1.05, $CHCl_3$)), the stereogenic center could be assigned as *R*. This configuration also correlated with the relative topicity previously observed in our group in the asymmetric synthesis of 2,3-dihydro-1*H*-isoindol-1-ones employing a related methodology.[15a] Moreover, a crystal structure of (2*S*,3*R*)-**3d** was obtained which allowed us to determine the absolute configuration with certainty, but the quality of the crystals did not allow a further refinement of the crystallographic data.[15b]

Access to 3-substituted 1,2,3,4-tetrahydroisoquinolines **6a** and **6c–f** was easily accomplished using an excess of the borane-tetrahydrofuran complex. This method is known to reduce carbonyl groups of amides[29] and hydrazines to amines by reductive N–N bond cleavage.[30] Each of hydrazines **3a** and **3c–f** was successfully cleaved in moderate to good yields without racemization. The results obtained are summarized in Table 5.

Table 5 N–N Cleavage of **3a** and **3c–f** with BH_3·THF to form 1,2,3,4-Tetrahydroisoquinolines **6a** and **6c–f**

6	R^1	R^2	Yield (%)	ee[a] (%)
(*S*)-**6a**	H	Phenyl	85[b]	≥97
(*R*)-**6c**	H	*p*-Methoxyphenyl	76	≥97
(*R*)-**6d**	H	Ferrocenyl	35	≥97
(*S*)-**6e**	H	Furan-2-yl	47[c]	≥99
(*R*)-**6f**	CH_3	Ferrocenyl	67	≥97

[a] Determined by HPLC on a chiral stationary phase.
[b] (2*R*,3*S*)-**3a** was used as starting material.
[e] (2*R*,3*S*)-**3e** was used as starting material.

In summary, the asymmetric synthesis of the title compounds has been achieved by a tandem 1,2-addition/ring closure protocol in moderate to good yields and high enantiomeric excesses (ee = 85–99%) employing lithiated *N*,*N*-diethyl-2-methylbenzamides and aldehyde SAMP- or RAMP-hydrazones as easily available substrates. The advantages of this entry are the high asymmetric inductions and the various N–N bond cleavage conditions to remove the chiral auxiliary.

All chemicals were purchased from commercial sources and used without further treatment unless otherwise indicated. Solvents were dried using standard procedures, and reactions requiring anhydrous conditions were performed under argon. All melting points were measured on a Büchi 510 (Dr. Tottoli system) melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer P241 polarimeter. NMR spectra were recorded on a Varian VXR 300, Varian Gemini 300, Varian Inova 400 or Varian Unity 500 spectrometer using Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 1760 spectrophotometer. MS spectra were recorded on a Finnigan SSQ7000 mass spectrometer. HRMS spectra were recorded on a Finnigan MAT95 mass spectrometer. Elementary analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Preparative column chromatography: Silica gel 60, particle size 0.040–0.063 mm, Merck. Analytical TLC: Pre-coated F_{254} silica gel 60 plates, Merck, Darmstadt.

***N*,*N*-Diethyl-2-methylbenzamide (1a)**
To a solution of diethylamine (22.71 g, 311 mmol) and Et_3N (31.42 g, 311 mmol) in Et_2O (500 mL) cooled to 0 °C was slowly added 2-methylbenzoyl chloride (48.0 g, 311 mmol). Upon completion of the addition the precipitate was filtered off, washed with Et_2O (100 mL) and discarded. The combined organic layers were concentrated under vacuum and the crude product was recrystallized from hexanes to give **1a** (57.58 g, 97%) as a colorless crystalline solid.

Mp 48 °C (lit.[31] 49–50 °C).

MS (EI): *m*/*z* (%) = 191 (M^+, 26), 190 (31), 176 (23), 120 (9), 119 (

[$M^+ - N(CH_2CH_3)_2$, 100], 118 (16), 91 (33), 65 (9).

The other analytical data correspond with those of the literature.[31,32]

***N*,*N*-Diethyl-2,5-dimethylbenzamide (1b)**
To a solution of 2,5-dimethylbenzoic acid (50.0 g, 330 mmol) and DMF (0.7 mL, 9 mmol) in CH_2Cl_2 (650 mL) was added a solution of oxalyl chloride (44.20 g, 350 mmol) in CH_2Cl_2 (500 mL). The reaction mixture was stirred for 1 h at r.t. (gas evolution allows to monitor the reaction). Upon removal of the solvent, the residue was purified by distillation to give 2,5-dimethylbenzoyl chloride (35.60 g, 75%); bp 84–86 °C/3 mbar (lit.[33] 89–90 °C/2 Torr).

To a solution of diethylamine (15.36 g, 210 mmol) and Et_3N (21.25 g, 210 mmol) in Et_2O (400 mL) cooled to 0 °C was slowly added 2,5-dimethylbenzoyl chloride (35.30 g, 209 mmol). At the end of addition the precipitate was filtered off, washed with Et_2O (100 mL) and discarded. The combined organic layers were concentrated under vacuum and the crude product was distilled under reduced pressure to give **1b** (40.20 g, 94%) as a colorless liquid.

Bp 117–120 °C/3 mbar (lit.[34] 108–115 °C/1 Torr).

The analytical data correspond with those of the literature.[34]

SAMP- or RAMP-Hydrazones 2a–e; General Procedure (GP 1)
RAMP or SAMP (1 equiv) was added to the aldehyde (1.2–2.4 equiv) at 0 °C. This mixture was stirred for 30 min at 0 °C followed by dilution with Et_2O (4.2 mL/mmol SAMP or RAMP). $MgSO_4$ was then added and the mixture was stirred overnight at r.t. After filtration and concentration in vacuum, the oily crude hydrazones were purified by distillation under reduced pressure.

(2*S*)-2-(Methoxymethyl)-*N*-[(1*E*)-phenylmethylene]pyrrolidin-1-amine [(*S*)-2a]
Compound **(*S*)-2a** was prepared earlier in our group.[17c]

(2*R*)-2-(Methoxymethyl)-*N*-[(1*E*)-phenylmethylene]pyrrolidin-1-amine [(*R*)-2a]

Compound **(*R*)-2a** was prepared earlier in our group.[17c]

(2*S*)-*N*-[(1*E*)-(4-Bromophenyl)methylene]-2-(methoxymethyl)pyrrolidin-1-amine [(*S*)-2b]

According to the general procedure GP 1, 4-bromo-benzaldehyde (10.0 g, 54 mmol) and SAMP (4.03 mL, 30 mmol) were reacted over night. After Kugelrohr distillation under high vacuum, (*S*)-**4b** (8.36 g, 94%) was obtained as a colorless solid.

Bp 130 °C/0.1–0.01 mbar; mp 38 °C; $[\alpha]_D^{25} = -144.8$ (c = 1.01, $CHCl_3$).

IR (KBr): 3427, 3082, 3054, 2979, 2920, 2875, 2825, 2808, 1914, 1580, 1549, 1483, 1459, 1397, 1376, 1342, 1304, 1279, 1246, 1193, 1126, 1094, 1068, 1005, 969, 878, 822, 708, 513 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.41–1.53 (m, 1 H, NCH_2CH_2), 1.63–1.78 (m, 3 H, $NCH_2CH_2CH_2$), 2.58–2.64 (m, 1 H, NCH_2), 2.94–3.01 (m, 1 H, NCH_2), 3.14 (s, 3 H, OCH_3), 3.37 (dd, 1 H, *J* = 7.0, 9.1 Hz, CH_2OCH_3), 3.60 (dd, 1 H, *J* = 3.6, 9.1 Hz, CH_2OCH_3), 3.64–3.71 (m, 1 H, $NCHCH_2OCH_3$), 6.83 (s, 1 H, N=C*H*), 7.34 (s, 4 H, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.4, 27.2, 48.3, 58.9, 63.2, 75.0, 120.4, 127.0, 129.5, 131.8, 137.2.

MS (CI, isobutane): *m*/*z* (%) = 300 (15), 299 [$M(^{81}Br)H^+$, 96], 298 (22), 297 [$M(^{78}Br)H^+$, 100], 296 (7), 220 (7), 219 (45), 218 (5).

Anal. Calcd for $C_{13}H_{17}BrN_2O$: C, 52.54; N, 9.43; H, 5.77. Found: C, 52.54; N, 9.31; H, 5.76.

(2*S*)-2-(Methoxymethyl)-*N*-[(1*E*)-(4-methoxyphenyl)methylene]pyrrolidin-1-amine [(*S*)-2c]

According to the general procedure GP 1, 4-methoxy-benzaldehyde (7.5 mL, 62 mmol) and SAMP (3.5 mL, 26 mmol) were reacted over night. After Kugelrohr distillation under high vacuum, (*S*)-**2c** (5.93 g, 91%) was obtained as a yellow solid.

Bp 115 °C/0.1–0.01 mbar; mp 24 °C (lit.[15] 24 °C); $[\alpha]_D^{23} = -150.2$ (c = 1.08, $CHCl_3$).

All other analytical data correspond to those of the enantiomer (*R*)-**2c**.[15]

(2*R*)-2-(Methoxymethyl)-*N*-[(1*E*)-(4-methoxyphenyl)methylene]pyrrolidin-1-amine [(*R*)-2c]

Compound (*R*)-**2c** was prepared earlier in our group.[15]

(2*S*)-*N*-[(1*E*)-1-(Ferrocenyl)methylene]-2-(methoxymethyl)pyrrolidin-1-amine [(*S*)-2d]

Compound (*S*)-**2d** was prepared earlier in our group.[17a]

(2*R*)-*N*-[(1*E*)-1-(Ferrocenyl)methylene]-2-(methoxymethyl)pyrrolidin-1-amine [(*R*)-2d]

Compound (*R*)-**2d** was prepared earlier in our group.[17b]

(2*S*)-*N*-[(1*E*)-1-(Furan-2-yl)methylene]-2-(methoxymethyl)pyrrolidin-1-amine [(*S*)-2e]

According to the general procedure GP 1, furan-2-carbaldehyde (9 mL, 110 mmol) and SAMP (8 mL, 60 mmol) were reacted over night. After distillation under high vacuum, (*S*)-**2e** (10.0 g, 80%) was obtained as a yellow oil.

Bp 90 °C/0.1–0.01 mbar; $[\alpha]_D^{25} = -132.4$ (c = 1.01, $CHCl_3$).

IR (capillary): 3114, 2974, 2926, 2878, 2827, 1602, 1580, 1566, 1545, 1490, 1480, 1459, 1392, 1342, 1323, 1306, 1285, 1270, 1228, 1196, 1162, 1121, 1075, 1012, 973, 932, 884, 732 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.38–1.49 (m, 1 H, NCH_2CH_2), 1.59–1.73 (m, 3 H, $NCH_2CH_2CH_2$), 2.54–2.61 (m, 1 H, NCH_2), 2.90–2.97 (m, 1 H, NCH_2), 3.11 (s, 3 H, OCH_3), 3.39 (dd, 1 H, *J* = 7.0, 9.1 Hz, CH_2OCH_3), 3.61 (dd, 1 H, *J* = 3.6, 9.1 Hz, CH_2OCH_3), 3.65–3.71 (m, 1 H, NC*H*), 6.20 (dd, 1 H, *J* = 1.8, 3.3 Hz, OCH=C*H*), 6.46 (d, 1 H, *J* = 3.3 Hz, OC=C*H*), 7.04 (s, 1 H, N=C*H*), 7.16 (dd, 1 H, *J* = 0.8, 1.8 Hz, OC*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 22.3, 27.2, 48.3, 58.8, 63.1, 74.9, 104.9, 111.5, 122.1, 141.1, 153.9.

MS (EI): *m*/*z* (%) = 208 (M^+, 23), 164 (10), 163 ($M^+ - CH_3OCH_2$, 100), 94 (11), 70 (12), 45 (6).

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; N, 13.45; H, 7.74. Found: C, 63.29; N, 13.46; H, 7.73.

(2*R*)-*N*-[(1*E*)-1-(Furan-2-yl)methylene]-2-(methoxymethyl)pyrrolidin-1-amine [(*R*)-2e]

According to the general procedure GP 1, furan-2-carbaldehyde (3.5 mL, 36.7 mmol) and RAMP (2.7 mL, 20.0 mmol) were reacted over night. After Kugelrohr distillation under high vacuum, (*R*)-**2e** (3.3 g, 79%) was obtained as a yellow oil.

Bp 120 °C/0.1–0.01 mbar; $[\alpha]_D^{24} = +125.0$ (c = 1.01, $CHCl_3$).

All other analytical data correspond to those of the enantiomer (*S*)-**2e**.

1,2-Addition/Ring Closure to Afford 3,4-Dihydro-2*H*-isoquinolin-1-ones 3a–f; General Procedure (GP 2)

n-BuLi (6.57 mL, 10.5 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (1.48 mL, 10.5 mmol) in absolute THF (50 mL) at 0 °C. The solution was stirred 15 min at 0 °C and cooled to –45 °C before a solution of *N*,*N*-diethylbenzamide **1a** or **1b** (10.5 mmol) in absolute THF (10 mL) was added. A solution of hydrazone **2a–e** (1.5 mmol) in absolute THF (6 mL) with or without $AlMe_3$ (0.83 mL, 1.65 mmol, 2 M in heptane) was added and the reaction mixture was stirred overnight at –40 °C. The reaction was quenched with a 10% solution of potassium and sodium tartrate (5 mL) and sat. aq NH_4Cl (10 mL). After phase separation, the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

(3*R*)-2-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one [(2*S*,3*R*)-3a]

According to the general procedure GP 2, (*S*)-**2a** and **1a** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 55:45), (2*S*,3*R*)-**3a** (355 mg, 70%) was obtained as a pale yellow oil which crystallized on standing as a colorless solid.

Mp 81 °C; R_f = 0.68 (Et_2O–hexanes, 2:1); $[\alpha]_D^{24} = -29.7$ (c = 1.02, $CHCl_3$).

IR (capillary): 2971, 2934, 2873, 1652, 1634, 1603, 1494, 1458, 1427, 1406, 1382, 1293, 1099, 769, 735, 701 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 1.25–1.33 (m, 1 H, $NCH_2CH_2CH_2$), 1.35–1.46 (m, 1 H, $NCH_2CH_2CH_2$), 1.81–1.89 (m, 1 H, $NCH_2CH_2CH_2$), 2.02–2.10 (m, 1 H, $NCH_2CH_2CH_2$), 2.67 (dd, 1 H, *J* = 2.7, 15.6 Hz, O=CNCHC*H*$_2$), 2.84 (td, 1 H, *J* = 7.8, 4.2 Hz, NCH_2), 3.16 (s, 3 H, OCH_3), 3.19 (dd, 1 H, *J* = 4.6, 9.4 Hz, CH_2OCH_3), 3.35 (dd, 1 H, *J* = 7.5, 9.4 Hz, CH_2OCH_3), 3.51 (dd, 1 H, *J* = 7.0, 15.6 Hz, O=CNCHC*H*$_2$), 3.96 (dd, 1 H, *J* = 7.8, 15.9 Hz, NCH_2), 4.36–4.41 (m, 1 H, $CHCH_2OCH_3$), 5.07 (dd, 1 H, *J* = 2.7, 7.0 Hz, O=CNC*H*), 6.60 (d, 1 H, *J* = 7.3 Hz, O=CCCC*H*), 6.93–7.00 (m, 4 H, CH_{arom}), 7.02–7.07 (m, 1 H, CH_{arom}), 7.09–7.13 (m, 2 H, CH_{arom}), 8.49 (dd, 1 H, *J* = 1.2, 7.6 Hz, O=CCC*H*).

^{13}C NMR (125 MHz, C_6D_6): δ = 23.5, 27.6, 36.9, 52.2, 58.6, 60.5, 66.4, 77.9, 127.0, 127.1, 127.4, 127.5, 128.1, 128.5, 131.5, 131.7, 135.7, 142.5, 162.9.

MS (EI): *m/z* (%) = 336 (M^+, 1), 304 (6), 292 (21), 291(M^+ – CH_3OCH_2, 100), 224 (7), 222 (8), 207 (23), 179 (7), 178 (12), 114 (55), 113 (10), 83 (5), 68 (6), 57 (5).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; N, 8.33; H, 7.19. Found: C, 74.91; N, 8.31; H, 7.33.

(3*R*)-3-(4-Bromophenyl)-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-3,4-dihydroisoquinolin-1(2*H*)-one [(2*S*,3*R*)-3b]

According to the general procedure GP 2, (*S*)-**2b** and **1a** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 1:1), (2*S*,3*R*)-**3b** (403 mg, 65%) was obtained as a colorless solid.

Mp = 79 °C; R_f = 0.39 (Et_2O–hexanes, 3:2); $[\alpha]_D^{23}$ = –17.3 (c = 1.02, $CHCl_3$).

IR (KBr): 2969, 2932, 2873, 2824, 1655, 1488, 1459, 1388, 1326, 1241, 1118, 1010, 742 cm^{-1}.

^1H NMR (300 MHz, C_6D_6): δ = 1.19–1.32 (m, 1 H, $NCH_2CH_2CH_2$), 1.33–1.49 (m, 1 H, $NCH_2CH_2CH_2$), 1.79–1.92 (m, 1 H, $NCH_2CH_2CH_2$), 1.96–2.10 (m, 1 H, $NCH_2CH_2CH_2$), 2.56 (dd, 1 H, *J* = 3.0, 15.8 Hz, O=CNCHCH_2), 2.76 (td, 1 H, *J* = 7.6, 4.3 Hz, NCH_2), 3.15 (s, 3 H, OCH_3), 3.12–3.19 (m, 1 H, CH_2OCH_3), 3.29 (dd, 1 H, *J* = 7.6, 9.2 Hz, CH_2OCH_3), 3.44 (dd, 1 H, *J* = 6.8, 15.8 Hz, O=CNCHCH_2), 3.86 (dd, 1 H, *J* = 7.9, 15.9 Hz, NCH_2), 4.25–4.36 (m, 1 H, $CHCH_2OCH_3$), 4.96 (dd, 1 H, *J* = 6.8, 2.9 Hz, O=CNC*H*), 6.65 (d, 1 H, *J* = 7.0 Hz, O=CCCC*H*), 6.77–6.83 (m, 2 H, CH_{arom}), 6.99–7.11 (m, 4 H, CH_{arom}), 8.42 (dd, 1 H, *J* = 1.5, 7.6 Hz, O=CCC*H*).

^{13}C NMR (75 MHz, C_6D_6): δ = 23.5, 27.5, 36.6, 52.3, 58.5, 60.5, 65.7, 77.7, 121.3, 127.2, 127.5, 128.1, 128.8, 131.2, 131.6, 131.9, 135.4, 141.5, 162.7.

MS (EI): *m/z* (%) = 416 [M(^{81}Br)$^+$, 0.2], 414 [M(^{79}Br)$^+$, 0.2], 372 (14), 371 [M(^{81}Br)$^+$ –CH_3OCH_2, 64], 370 (14), 369 [M(^{79}Br)$^+$ – CH_3OCH_2, 66], 302 (8), 287 (10), 285 (10), 239 (5), 237 (5), 206 (13), 178 (19), 119 (6), 118 (5), 115 (7), 114 ($C_6H_{12}NO^+$ – H, 100), 113 (9), 91 (5), 90 (7), 89 (6), 83 (5), 70 (7), 68 (13), 45 (6).

Anal. Calcd for $C_{21}H_{23}BrN_2O_2$: C, 60.73; N, 6.74; H, 5.58. Found: C, 60.68; N, 6.73; H, 5.73.

(3*R*)-2-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-3-(4-methoxyphenyl)-3,4-dihydroisoquinolin-1(2*H*)-one [(2*S*,3*R*)-3c]

According to the general procedure GP 2, (*S*)-**2c** and **1a** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 1:1), (2*S*,3*R*)-**3c** (213 mg, 39%) was obtained as a colorless oil.

R_f = 0.42 (Et_2O–hexanes, 3:2); $[\alpha]_D^{23}$ = –36.4 (c = 1.08, $CHCl_3$).

IR ($CHCl_3$): 3068, 2951, 2875, 2835, 1651, 1611, 1583, 1512, 1461, 1427, 1402, 1334, 1305, 1251, 1179, 1158, 1102, 1036, 985, 967, 829, 814, 747 cm^{-1}.

^1H NMR (300 MHz, C_6D_6): δ = 1.25–1.53 (m, 2 H, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 1.80–1.94 (m, 1 H, $NCH_2CH_2CH_2$), 2.01–2.15 (m, 1 H, $NCH_2CH_2CH_2$), 2.67 (dd, 1 H, *J* = 2.8, 15.7 Hz, O=CNCHCH_2), 2.89 (td, 1 H, *J* = 6.8, 5.2 Hz, NCH_2), 3.17 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 3.15–3.24 (m, 1 H, CH_2OCH_3), 3.38 (dd, 1 H, *J* = 7.3, 9.2 Hz, CH_2OCH_3), 3.52 (dd, 1 H, *J* = 6.9, 15.7 Hz, O=CNCHCH_2), 3.97 (dd, 1 H, *J* = 7.8, 15.8 Hz, NCH_2), 4.33–4.45 (m, 1 H, $CHCH_2OCH_3$), 5.04 (dd, 1 H, *J* = 6.9, 2.8 Hz, O=CNC*H*), 6.53–6.59 (m, 2 H, CH_{arom}), 6.67 (d, 1 H, *J* = 7.4 Hz, O=CCCC*H*), 6.99–7.12 (m, 4 H, CH_{arom}), 8.51 (dd, 1 H, *J* = 1.5, 7.6 Hz, O=CCC*H*).

^{13}C NMR (75 MHz, C_6D_6): δ = 23.5, 27.6, 37.0, 52.2, 54.6, 58.6, 60.5, 65.9, 77.8, 113.9, 127.1, 127.6, 128.0, 128.1, 131.6, 131.8, 134.3, 136.0, 159.3, 162.9.

MS (CI, isobutane): *m/z* (%) = 368 (24), 367 (MH^+, 100).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; N, 7.64; H, 7.15. Found: C, 71.99; N, 7.52; H, 7.64.

(3*R*)-3-Ferrocenyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-3,4-dihydroisoquinolin-1(2*H*)-one [(2*S*,3*R*)-3d]

According to the general procedure GP 2, (*S*)-**2d** and **1a** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 9:11) and recrystallization from petroleum ether (2*S*,3*R*)-**3d** (418 mg, 63%) was obtained as orange-red crystals.

Mp 150 °C; R_f = 0.37 (Et_2O–hexanes, 1:1); $[\alpha]_D^{24}$ = +197.4 (c = 1.01, $CHCl_3$).

IR (KBr): 3087, 2966, 2918, 2873, 1649, 1602, 1458, 1389, 1310, 1249, 1154, 1132, 1096, 842, 813, 743, 706 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.34–1.44 (m, 1 H, $NCH_2CH_2CH_2$), 1.53–1.64 (m, 1 H, $NCH_2CH_2CH_2$), 1.92–2.11 (m, 2 H, $NCH_2CH_2CH_2$), 3.09–3.28 (m, 3 H, O=CNCHCH_2, NCH_2, CH_2OCH_3), 3.17 (s, 3 H, OCH_3), 3.42 (dd, 1 H, *J* = 6.9, 9.3 Hz, CH_2OCH_3), 3.53–3.55 (m, 1 H, $NCHC_5H_4$), 3.59 (dd, 1 H, *J* = 6.9, 15.5 Hz, O=CNCHCH_2), 3.66–3.68 (m, 1 H, $NCHC_5H_4$), 3.78–3.86 (m, 2 H, NCH_2, $NCHC_5H_4$), 3.97 [s, 5 H, $NCH(C_5H_4)Fe(C_5H_5)$], 4.26–4.35 (m, 2 H, $CHCH_2OCH_3$, $NCHC_5H_4$), 4.77 (dd, 1 H, *J* = 6.9, 1.9 Hz, O=CNC*H*), 6.96 (d, 1 H, *J* = 7.4 Hz, O=CCCC*H*), 7.02–7.07 (m, 1 H, CH_{arom}), 7.12–7.17 (m, 1 H, CH_{arom}), 8.43 (dd, 1 H, *J* = 1.4, 7.7 Hz, O=CCC*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 23.7, 27.9, 34.9, 52.6, 58.5, 60.8, 62.1, 66.3, 67.4, 68.4, 68.8, 70.2, 77.6, 89.8, 126.7, 126.8, 128.3, 131.1, 131.5, 137.4, 161.6.

MS (EI): *m/z* (%) = 445 (5), 444 (M^+, 20), 399 (M^+ – CH_3OCH_2, 16), 333 (6), 332 (20), 331 (M^+ – $C_6H_{12}NO$ + H, 100), 330 (19), 329 (55), 328 (8), 266 (10), 265 (17), 264 (23), 263 (7), 248 (5), 237 (6), 221 (7), 213 (6), 199 (9), 186 (9), 177 (5), 166 (7), 165 (20), 120 (9), 83 (16), 82 (6), 70 (6), 68 (5), 59 (7), 58 (19), 55 (5).

Anal. Calcd for $C_{25}H_{28}FeN_2O_2$: C, 67.57; N, 6.30; H, 6.35. Found: C, 67.66; N, 6.21; H, 6.44.

(3*S*)-3-Furan-2-yl-2-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]-3,4-dihydroisoquinolin-1(2*H*)-one [(2*R*,3*S*)-3e]

According to the general procedure GP 2, (*R*)-**2e** and **1a** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 9:11) and recrystallization from hexanes (2*R*,3*S*)-**3e** (220 mg, 45%) was obtained as brown needles.

Mp 61 °C; R_f = 0.41 (Et_2O–hexanes, 9:11); $[\alpha]_D^{27}$ = +96.0 (c = 0.81, $CHCl_3$).

IR (capillary): 2968, 2874, 1656, 1605, 1460, 1402, 1380, 1325, 1246, 1137, 1102, 1012, 742 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.25–1.35 (m, 1 H, $NCH_2CH_2CH_2$), 1.47–1.58 (m, 1 H, $NCH_2CH_2CH_2$), 1.89–2.00 (m, 1 H, $NCH_2CH_2CH_2$), 2.01–2.10 (m, 1 H, $NCH_2CH_2CH_2$), 2.84 (dd, 1 H, *J* = 2.6, 15.8 Hz, O=CNCHCH_2), 3.09 (s, 3 H, OCH_3), 3.07–3.17 (m, 2 H, NCH_2, CH_2OCH_3), 3.28 (dd, 1 H, *J* = 7.7, 9.3 Hz, CH_2OCH_3), 3.40 (dd, 1 H, *J* = 6.4, 15.7 Hz, O=CNCHCH_2), 3.96 (dd, 1 H, *J* = 8.0, 15.7 Hz, NCH_2), 4.25–4.34 (m, 1 H, $CHCH_2OCH_3$), 5.12 (dd, 1 H, *J* = 6.4, 2.6 Hz, O=CNC*H*), 5.86–5.91 (m, 2 H, OC=C*HCH*), 6.68–6.72 (m, 1 H, O=CCCC*H*), 6.91 (dd, 1 H, *J* = 1.9, 0.8 Hz, OC*H*=CH), 6.98–7.05 (m, 2 H, CH_{arom}), 8.41–8.43 (m, 1 H, O=CCC*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 23.7, 27.7, 34.0, 52.3, 58.5, 60.7, 77.8, 106.9, 110.2, 126.9, 127.2, 128.1, 131.0, 131.5, 136.1, 141.6, 155.1, 162.4.

MS (EI): *m/z* (%) = 326 (M^+, 0.6), 294 (17), 282 (19), 281 (M^+ – CH_3OCH_2, 100), 195 (5), 169 (12), 141 (13), 115 (6), 114 (19), 45 (5).

Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; N, 8.58; H, 6.79. Found: C, 69.84; N, 8.65; H, 6.89.

(3*S*)-3-Ferrocenyl-2-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]-7-methyl-3,4-dihydroisoquinolin-1(2*H*)-one [(2*R*,3*S*)-3f]

According to the general procedure GP 2, (*R*)-**2d** and **1b** were reacted over night. After purification by column chromatography (Et_2O–hexanes, 9:11) and recrystallization (CH_2Cl_2–hexanes mixture) (2*R*,3*S*)-**3f** (317 mg, 46%) was obtained as orange-red crystals.

Mp 165 °C; R_f = 0.42 (Et_2O–hexanes, 1:1); $[\alpha]_D^{22}$ = –219.3 (c = 1.00, $CHCl_3$).

IR (KBr): 3432, 2957, 2873, 1648, 1612, 1426, 1387, 1313, 1254, 1128, 1097, 818 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.36–1.47 (m, 1 H, $NCH_2CH_2CH_2$), 1.54–1.65 (m, 1 H, $NCH_2CH_2CH_2$), 1.93–2.12 [m, 5 H, $NCH_2CH_2CH_2$, O=CCCH=C(CH_3)], 3.18 (s, 3 H, OCH_3), 3.11–3.28 (m, 3 H, O=CNCHCH_2, NCH_2, CH_2OCH_3), 3.43 (dd, 1 H, *J* = 6.9, 9.3 Hz, CH_2OCH_3), 3.57–3.64 (m, 2 H, $NCHC_5H_4$, O=CNCHCH_2), 3.68–3.71 (m, 1 H, $NCHC_5H_4$), 3.80–3.88 (m, 2 H, NCH_2, $NCHC_5H_4$), 3.99 [s, 5 H, NCH(C_5H_4)Fe(C_5H_5)], 4.27–4.37 (m, 2 H, $CHCH_2OCH_3$, $NCHC_5H_4$), 4.78 (dd, 1 H, *J* = 6.9, 1.9 Hz, O=CNC*H*), 6.93 (d, 1 H, *J* = 7.7 Hz, CH_{arom}), 7.07 (dd, 1 H, *J* = 7.7, 14 Hz, CH_{arom}), 8.18 (d, 1 H, *J* = 1.7 Hz, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 20.9, 23.7, 27.9, 34.6, 52.5, 58.5, 60.7, 62.2, 66.4, 67.3, 68.3, 68.8, 70.2, 77.6, 89.8, 126.7, 128.8, 130.9, 132.3, 134.4, 136.3, 161.9.

MS (EI): *m*/*z* (%) = 459 (21), 458 (M^+, 69), 414 (16), 413 (M^+ – CH_3OCH_2, 55), 347 (14), 346 (21), 345 (83), 344 (25), 343 (48), 342 (5), 329 (6), 280 (18), 279 (30), 278 (100), 277 (6), 276 (7) 263 (20), 262 (9), 254 (7), 251 (5), 249 (5), 237 (5), 236 (8), 235 (16), 222 (5), 214 (8), 213 (6), 207 (7), 200 (17), 199 (88), 197 (7), 194 (6), 186 (19), 180 (23), 179 (49), 178 (19), 167 (11), 166 (13), 165 (31), 153 (5), 152 (8), 149 (12), 129 (10), 121 (43), 113 (7), 112 (6), 101 (5), 97 (6), 91 (5), 85 (7), 83 (8), 82 (5), 71 (11), 70 (14), 69 (7), 68 (5), 57 (16), 56 (14), 55 (13), 45 (18).

Anal. Calcd for $C_{26}H_{30}FeN_2O_2$: C, 68.13; N, 6.11; H, 6.60. Found: C, 67.84; N, 6.08; H, 6.55.

N–N Bond Cleavage with Lithium in Liquid Ammonia to Afford 3,4-Dihydroisoquinolines 4a and 4d; General Procedure (GP 3)

In a two-neck flask filled with Ar, liquid ammonia (50 mL/mmol hydrazine) was condensed at –78 °C. Freshly cut lithium (4.5–10 equiv), washed successively with MeOH and Et_2O, was added to the solution and a persisting deep blue color developed. After 5 min at –78 °C, the hydrazine **3a** or **3d** (1.0 equiv) in absolute THF (20 mL/mmol hydrazine) was added. The cooling bath was removed and the reaction mixture was stirred for 5 min at reflux (–33 °C) before being cooled again to –78 °C. The reaction was quenched by slowly adding solid NH_4Cl (1 g/mmol hydrazine). After evaporation of the ammonia, the residue was diluted in H_2O and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure.

N–N Bond Cleavage with Calcium in Liquid Ammonia to Afford 3,4-Dihydroisoquinolines 4a, 4d and 4e; General Procedure (GP 3)

In a two-neck flask filled with Ar, liquid ammonia (50 mL/mmol hydrazine) was condensed at –78 °C. Freshly cut calcium (2.2–3.5 equiv) was added to the solution and a persisting deep blue color slowly developed. The cooling bath was then removed to afford the ammonia solution to reflux (–33 °C) resulting in the formation of a metallic mirror on the flask wall. The reaction mixture was cooled again to –78 °C. The hydrazine **3a**, **3d** or **3e** (1.0 equiv) in absolute THF (20 mL/mmol hydrazine) was then slowly added. The cooling bath was removed and the reaction mixture was stirred for 5 min at reflux. The solution was cooled again to –78 °C. The reaction was quenched by slowly adding solid NH_4Cl (1 g/mmol hydrazine). After evaporation of the ammonia, the residue was diluted in H_2O and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum.

(3*S*)-3-Phenyl-3,4-dihydroisoquinoline [(*S*)-4a]

Compound (2*R*,3*S*)-**3a** (328 mg, 0.97 mmol) was reacted according to the general procedure GP 3 using calcium in liquid ammonia. After purification by column chromatography (Et_2O–hexanes, 6:4), (*S*)-**4a** (134 mg, 67%) was obtained as colorless crystals.

ee ≥96% (^1H NMR, (*R*)-(–)-anthr-9-yl-2,2,2-trifluoroethanol as shift-reagent).

Mp 58 °C (lit.[35] 80.5–81.5 °C, *rac*-**6a**); R_f = 0.31 (Et_2O–hexanes, 1:1); $[\alpha]_D^{23}$ = –129.8 (c = 1.00, $CHCl_3$).

^1H NMR (300 MHz, C_6D_6): δ = 2.50–2.69 (m, 2 H, NCHCH_2), 4.54 (ddd, 1 H, *J* = 3.0, 6.6, 13.1 Hz, NC*H*CH_2), 6.72–6.77 (m, 1 H, CH_{arom}), 6.84–6.89 (m, 1 H, CH_{arom}), 6.93–7.05 (m, 2 H, CH_{arom}), 7.09–7.17 (m, 1 H, CH_{arom}), 7.21–7.28 (m, 2 H, CH_{arom}), 7.45–7.51 (m, 2 H, CH_{arom}), 8.38 (d, 1 H, *J* = 3.0 Hz, N=C*H*).

^{13}C NMR (75 MHz, C_6D_6): δ = 34.2, 61.4, 126.9, 127.2, 127.3, 127.5, 127.6, 128.5, 128.9, 130.9, 136.4, 145.0, 159.7.

MS (EI): *m*/*z* (%) = 208 (17), 207 (M^+, 100), 206 (78), 180 (5), 179 (7), 178 (7), 130 (M^+ – C_6H_5), 103 (6), 102 (7), 90 (6), 89 (11).

All other analytical data correspond with those of the literature.[35]

(3*R*)-3-Ferrocenyl-3,4-dihydroisoquinoline [(*R*)-4d]

Compound (2*S*,3*R*)-**3d** (200 mg, 0.45 mmol) was reacted according to the general procedure GP 3 using lithium in liquid ammonia. After purification by column chromatography (Et_2O–hexanes, 2:1 + 0.5% Et_3N), (*R*)-**4d** (57 mg, 40%) was obtained as a red-brown oil which decomposed slowly even at –25 °C.

ee ≥96% (^1H NMR with (*R*)-(–)-anthr-9-yl-2,2,2-trifluoroethanol).

R_f = 0.70 (Et_2O).

IR (KBr): 3431, 3116, 3077, 2926, 2864, 2183, 1624, 1583, 1489, 1436, 1378, 1278, 1143, 1104, 1005, 905, 885, 831, 812, 756, 497 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 2.70–2.79 (m, 2 H, NCHCH_2), 4.02–4.05 (m, 2 H, $NCHC_5H_4$), 4.17 [m, 5 H, NCH(C_5H_4)Fe(C_5H_5)], 4.29–4.34 (m, 2 H, $NCHC_5H_4$), 4.36–4.43 (m, 1 H, NC*H*CH_2), 6.70–6.82 (m, 2 H, CH_{arom}), 6.94–7.00 (m, 1 H, CH_{arom}), 7.01–7.06 (m, 1 H, CH_{arom}), 8.32 (d, 1 H, *J* = 2.8 Hz, N=C*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 33.0, 56.4, 67.1, 67.4, 67.7, 67.8, 68.9, 126.9, 127.0, 127.4, 128.9, 130.6, 136.3, 158.2.

MS (EI): *m*/*z* (%) = 316 (23), 315 (M^+, 100), 314 (35), 313 (M^+ – H_2, 86), 311 (5), 250 (11), 249 (42), 248 (30), 186 (6), 166 (5), 165 (11), 121 (6).

A correct elementary analysis could not be obtained for this compound.

(3*S*)-3-Furan-2-yl-3,4-dihydroisoquinoline [(*S*)-4e]

Compound (2*R*,3*S*)-**3e** (155 mg, 0.48 mmol) was reacted according to the general procedure GP 3 using calcium in liquid ammonia. After purification by column chromatography (Et_2O–hexanes, 6:4), (*S*)-**4e** (30 mg, 32%) was obtained as a colorless oil.

R_f = 0.32 (Et_2O–hexanes = 2:1).

^1H NMR (400 MHz, C_6D_6): δ = 2.71–2.84 (m, 2 H, NCHCH_2), 4.68–4.74 (m, 1 H, NC*H*CH_2), 6.14 (dd, 1 H, *J* = 1.8, 3.2 Hz, OCH=C*H*), 6.39–6.41 (m, 1 H, OC=C*H*), 6.69–6.73 (m, 1 H,

CH_{arom}), 6.77–6.80 (m, 1 H, CH_{arom}), 6.88–6.99 (m, 1 H, CH_{arom}), 7.14–7.16 (m, 1 H, OC*H*=CH), 8.27 (d, 1 H, *J* = 2.7 Hz, N=C*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 30.3, 55.8, 106.0, 110.4, 127.1, 128.6, 130.9, 135.6, 141.5, 157.2, 159.7 (the two missing signals are under the solvent residual peak).

N–N Bond Cleavage to Afford 3,4-Dihydroisoquinolin-1(2*H*)-ones 5a, 5d and 5e; General Procedure (GP 4)

Method A

MeOH (60 mL/mmol hydrazine) and acetyl chloride (6.0 mL/mmol hydrazine) were mixed at 0 °C. This mixture was added to 3,4-dihydroisoquinolin-1(2*H*)-ones **3a**, **3d** or **3e** and the solvent was removed in vacuum. The residue was diluted with AcOH (75 mL/mmol hydrazine) and zinc powder (2.2 g/mmol hydrazine) and 6 N HCl (3 drops/mmol hydrazine) were successively added. After sonicating for 15 min, the reaction mixture was heated to reflux for 36 h, while new zinc powder was added every 12 h (3.0 g/mmol hydrazine). After allowing the reaction mixture to cool to r.t., the solid was filtered off and washed with H_2O and AcOH. The liquid was concentrated under reduced pressure. Sat. aq Na_2CO_3 was added to the residue until evolution of gas has ceased. The mixture was then extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and the solvent evaporated in vacuum.

Method B

A solution of **3a**, **3d** or **3e** (1.0 equiv) and MMPP·$6H_2O$ (2.0–2.5 equiv) in MeOH (13 mL/mmol hydrazine) was stirred at r.t. until the hydrazine was consumed (24–96 h, TLC control). If necessary, more MMPP·$6H_2O$ was added to the reaction mixture. The reaction mixture was diluted with Et_2O (60 mL/mmol hydrazine) and sat. aq $NaHCO_3$ (43 mL/mmol hydrazine) was added. The layers were separated and the aqueous phase was extracted 3 times with $CHCl_3$ or CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the solvent were evaporated in vacuum.

Method C[27]

A THF solution of SmI_2 (3.1 equiv, 0.1 M in THF) was added dropwise to a solution (6.9 mL/mmol hydrazine) of **3a** (1.0 equiv) and DMPU (1.75 mL/mmol hydrazine) in THF (7.3 mL/mmol hydrazine) at r.t. under Ar. After 30 min, the reaction mixture was quenched with a mixture of 10% $NaHCO_3$ (175 mL/mmol hydrazine) and CH_2Cl_2 (70 mL/mmol hydrazine), extracted 2 times with CH_2Cl_2 (100 mL/mmol hydrazine), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

(3*R*)-3-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one [(*R*)-5a]

According to the general procedure GP 4 (method B) (2*S*,3*R*)-**3a** (157 mg, 0.47 mmol) was reacted with MMPP·$6H_2O$. After purification by column chromatography (Et_2O–hexanes, 7:3) (*R*)-**5a** (74 mg, 71%) was obtained as a colorless solid.

ee ≥99% (HPLC, Daicel OD, *n*-heptane–*i*-PrOH, 95:5).

Mp 105 °C (lit.[5e] 130–131 °C); R_f = 0.67 (Et_2O); $[\alpha]_D^{23}$ = +195.3 (c = 1.05, $CHCl_3$).

According to the general procedure GP 4 (method C) (2*S*,3*R*)-**3a** (162 mg, 0.48 mmol) was reacted with SmI_2. After purification by column chromatography (*n*-pentane–Et_2O, 1:3) (*R*)-**5a** (102 mg, 93%) was obtained as a colorless solid.

ee ≥98% (HPLC, Chiracel OD, *n*-heptane–*i*-PrOH, 9:1).

^{1}H NMR (300 MHz, C_6D_6): δ = 2.56–2.73 (m, 2 H, NCHCH_2), 4.33–4.40 (m, 1 H, NC*H*CH$_2$), 6.66–6.71 (m, 1 H, O=CCCC*H*), 6.97–7.17 (m, 7 H, CH_{arom}), 8.14 (s, 1 H, N*H*), 8.28–8.35 (m, 1 H, O=CCC*H*).

^{13}C NMR (75 MHz, C_6D_6): δ = 37.3, 55.7, 126.7, 127.3, 127.4, 128.0, 128.5, 128.8, 129.6, 132.0, 137.9, 141.9, 166.2.

MS (EI): *m*/*z* (%) = 224 (13), 223 (M^+, 75), 222 (8), 194 (5), 146 (6), 145 (5), 119 (12), 118 ($M^+ - NH_2Bn$, 100), 90 (26), 89 (10).

All other analytical data correspond to those of the literature.[5e]

X-ray Crystallographic Study of (3*R*)-3-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one [(*R*)-5a]

Single crystals of (*R*)-**5a** were obtained by recrystallization from Et_2O. The compound crystallizes in the monoclinic space group $P2_1$ (Nr. 4) with two symmetrically independent molecules in the asymmetric unit ($2 \times C_{15}H_{13}NO$, M_r = 446.55). The cell dimensions are *a* = 9.087(1), *b* = 6.126(1), *c* = 20.915(3) Å, and β = 91.176(5)°. A cell volume of *V* = 1164.0(3) Å^3 and *Z* = 2 result in a calculated density of $\rho_{calc.}$ = 1.274 gcm^{-3}. 4959 reflections have been collected in the ω/2Θ mode at T = 298 K on an Enraf-Nonius CAD4 diffractometer employing graphite monochromated CuK_α-radiation (λ = 1.54179 Å). Data collection covered the range $-11 \le h \le 11$, $-7 \le k \le 7$, and $-25 \le l \le 25$ (Friedel pairs) up to Θ_{max} = 72.77°; μ = 0.63 mm^{-1}, no absorption correction. The structure has been solved by directs methods as implemented in the Xtal3.7 suite of crystallographic routines[36] where GENSIN has been used to generate the structure-invariant relationships and GENTAN for the general tangent phasing procedure. 3768 observed reflections ($I > 2\sigma(I)$) have been included in the final full matrix least-squares refinement on *F* involving 316 parameters and converging at $R(R_w)$ = 0.089 (0.11, $w = 1/[18.0\sigma^2(F)]$, S = 1.277, and a residual electron density of –0.36/0.50 eÅ^{-3}. Due to a large standard deviation the result of an attempted determination of the absolute configuration using Flack's method[37] turned out to be insignificant. However, based on chemical evidence the absolute configuration of the molecule could be assigned as shown in Figure 1. The nitrogen-bonded hydrogen atoms could be located and have been refined isotropically. All other hydrogen positions have been calculated in idealized positions, and their *U*s have been fixed at 1.5 times *U* of the relevant heavy atom without refinement of any parameters.

(3*S*)-3-Ferrocenyl-3,4-dihydroisoquinolin-1(2*H*)-one [(*S*)-5d]

According to the general procedure GP 3 (2*R*,3*S*)-**3d** (125 mg, 0.28 mmol) was reacted with calcium in liquid ammonia. After purification by column chromatography (Et_2O–hexanes, 2:1) (*S*)-**5d** (41 mg, 44%) was obtained as a orange-red solid.

ee = 95% (HPLC, Chiralpak AD, *n*-heptane–*i*-PrOH, 85:15).

Mp 128 °C; R_f = 0.49 (Et_2O); $[\alpha]_D^{23}$ = +61.3 (c = 0.60, $CHCl_3$).

IR (KBr): 3447, 3221, 3074, 2945, 2843, 2198, 1661, 1603, 1578, 1463, 1402, 1385, 1320, 813, 747 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 2.62–2.77 (m, 2 H, NCHCH_2), 3.83–3.86 [m, 1 H, NCH(C_5H_4)], 3.88–3.93 [m, 2 H, NCH(C_5H_4)], 4.07–4.18 [m, 7 H, NC*H*(C_5H_4)Fe(C_5H_5)], 6.73–6.79 (m, 1 H, O=CCCC*H*), 7.05–7.13 (m, 2 H, CH_{arom}), 8.00 (s, 1 H, N*H*), 8.53–8.58 (m, 1 H, O=CCC*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 37.1, 50.6, 66.2, 66.5, 68.0, 68.1, 69.0, 90.1, 127.1, 127.3, 128.1, 129.7, 131.8, 138.1, 165.8.

MS (EI): *m*/*z* (%) = 333 (8), 332 (23), 331 (M^+, 100), 330 (16), 329 (47), 328 (8), 266 (6), 265 (10), 264 (8), 263 (6), 213 (5), 186 (7), 165 (9).

Anal. Calcd for $C_{19}H_{17}FeNO$: C, 68.90; N, 4.23; H, 5.17. Found: C, 68.41; N, 4.01; H, 5.30.

(3*R*)-3-Furan-2-yl-3,4-dihydroisoquinolin-1(2*H*)-one [(*R*)-5e]

According to the general procedure GP 4 (method B) (2*S*,3*R*)-**3e** (224 mg, 0.69 mmol) was reacted with MMPP·$6H_2O$. After purification by column chromatography (Et_2O–hexanes, 7:3) and recrystallization (Et_2O–hexanes–CH_2Cl_2 mixture), (*R*)-**5e** (20 mg, 14%) was obtained as a colorless solid.

ee ≥98% (HPLC, Daicel OD, *n*-heptane–*i*-PrOH, 97:3).

Mp 97 °C; R_f = 0.17 (Et_2O–hexanes, 2:1); $[\alpha]_D^{25}$ = +30.5 (c = 0.56, $CHCl_3$).

IR (KBr): 3177, 3069, 3034, 1660, 1607, 1576, 1468, 1395, 1318, 1006, 817, 788, 736 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 2.71 (dd, 1 H, *J* = 5.2, 15.7 Hz, NCHCH_2), 2.84 (dd, 1 H, *J* = 7.7, 15.7 Hz, NCHCH_2), 4.34–4.40 (m, 1 H, NC*H*CH_2), 5.92 (dd, 1 H, *J* = 1.8, 3.2 Hz, OCH=C*H*), 6.03–6.07 (m, 1 H, OC=C*H*), 6.65–6.70 (m, 1 H, O=CCCC*H*), 6.94 (dd, 1 H, *J* = 0.8, 1.6 Hz, OC*H*=CH), 6.97–7.03 (m, 2 H, CH_{arom}), 7.92 (m, 1 H, N*H*), 8.38–8.44 (m, 1 H, O=CCC*H*).

^{13}C NMR (100 MHz, C_6D_6): δ = 33.1, 49.2, 106.6, 110.3, 127.1, 127.4, 128.2, 129.2, 131.9, 137.2, 141.8, 154.3, 165.8.

MS (EI): *m*/*z* (%) = 214 (5), 213 (M^+, 32), 212 (5), 196 (15), 195 (99), 184 (15), 156 (6), 128 (7), 119 (10), 118 (100), 91 (5), 90 (39), 89 (14).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; N, 6.57; H, 5.20. Found: C, 73.32; N, 6.55; H, 5.43.

N–N Bond Cleavage Using BH_3·THF to Afford 1,2,3,4-Tetrahydroisoquinolines 6a and 6c-f; General Procedure (GP 5)

In a Schlenk flask filled with Ar and fitted with a condenser was placed a solution of the hydrazine (1.0 equiv) in absolute THF (40 mL/mmol hydrazine). BH_3·THF (20 equiv, 1 M in THF) was added and the reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to –5 °C and a solution of 1 N HCl (7.7 mL/mmol hydrazine) was cautiously added. After a 1 min reflux, the solvent was removed in vacuum and sat. aq solution of $NaHCO_3$ or K_2CO_3 was added to the residue until no evolution of gas could be observed. The mixture was extracted 3 times with CH_2Cl_2 or Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and evaporated in vacuum.

(3*S*)-3-Phenyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-6a]

According to the general procedure GP 5 (2*R*,3*S*)-**3a** (809 mg, 2.40 mmol) was reacted with BH_3·THF (48.1 mL, 48.1 mmol). After purification by column chromatography (*n*-pentane– Et_2O, 7:3) (*S*)-**6a** (430 mg, 85%) was obtained as a pale yellow oil.

ee ≥97% (HPLC, Chiralcel OJ, *n*-heptane–*i*-PrOH, 98:2).

R_f = 0.31 (Et_2O–hexanes, 4:6); $[\alpha]_D^{25}$ = +26.7 (c = 1.10, $CHCl_3$).

^1H NMR (400 MHz, C_6D_6): δ = 1.18 (br s, 1 H, N*H*), 2.68 (dd, 1 H, *J* = 3.8, 15.9 Hz, NHCHCH_2), 2.81 (dd, 1 H, *J* = 10.7, 15.9 Hz, NHCHCH_2), 3.64 (dd, 1 H, *J* = 4.0, 10.7 Hz, NHC*H*CH_2), 3.80–3.90 (m, 2 H, CH_2NH), 6.85–6.92 (m, 2 H, CH_{arom}), 7.02–7.07 (m, 2 H, CH_{arom}), 7.10–7.15 (m, 1 H, CH_{arom}), 7.18–7.23 (m, 2 H, CH_{arom}), 7.31–7.35 (m, 2 H, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 38.5, 49.3, 58.7, 125.9, 126.2, 126.4, 127.0, 127.4, 128.6, 129.3, 135.5, 135.7, 145.4.

All other analytical data are consistent with those reported in the literature.[38]

(3*R*)-3-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline [(*R*)-6c]

According to the general procedure GP 5 (2*S*,3*R*)-**3c** (118 mg, 0.32 mmol) was reacted with BH_3·THF (6.4 mL, 6.4 mmol). After purification by column chromatography (Et_2O–hexanes, 99:1 + 1% Et_3N) (*R*)-**6c** (58 mg, 76%) was obtained as a colorless solid.

ee ≥97% (HPLC, Daicel AD, *n*-heptane–*i*-PrOH, 95:5).

Mp 91 °C; R_f = 0.23 (Et_2O); $[\alpha]_D^{26}$ = +119.1 (c = 1.39, $CHCl_3$).

IR (KBr): 3447, 3221, 3016, 2957, 2936, 2907, 2885, 2861, 2835, 1610, 1581, 1511, 1453, 1438, 1413, 1385, 1353, 1298, 1244, 1196, 1182, 1118, 1103, 1040, 1025, 963, 938, 914, 874, 831, 810, 778, 743 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.31 (br s, 1 H, N*H*), 2.72 (dd, 1 H, *J* = 3.7, 15.9 Hz, NHCHCH_2), 2.86 (dd, 1 H, *J* = 10.7, 15.9 Hz, NHCHCH_2), 3.36 (s, 3 H, OCH_3), 3.60 (dd, 1 H, *J* = 4.0, 10.7 Hz, NHC*H*), 3.84–3.95 (m, 2 H, CH_2NH), 6.82–6.97 (m, 4 H, CH_{arom}), 7.03–7.08 (m, 2 H, CH_{arom}), 7.25–7.30 (m, 2 H, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 38.5, 49.4, 54.7, 58.1, 113.9, 125.7, 126.0, 126.2, 127.8, 129.1, 135.4, 135.6, 137.3, 159.1.

MS (EI): *m*/*z* (%) = 240 (17), 239 (M^+, 100), 238 (54), 224 (16), 222 (7), 208 (11), 134 (15), 132 (9), 131 (9), 130 (12), 121 (19), 105 (13), 104 (78), 103 (15), 78 (12), 77 (7).

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO$: 239.1310; found: 239.1310.

(3*R*)-3-Ferrocenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-6d]

According to the general procedure GP 5 (2*S*,3*R*)-**3d** (330 mg, 0.74 mmol) was reacted with BH_3·THF (14.8 mL, 14.8 mmol). After purification by column chromatography (Et_2O–hexanes, 3:6) (*S*)-**6d** (83 mg, 35%) was obtained as a orange-red solid.

ee ≥97% (HPLC, Chiralpak AD, *n*-heptane–*i*-PrOH, 93:7).

Mp 80 °C; R_f = 0.13 (Et_2O); $[\alpha]_D^{25}$ = +69.7 (c = 1.02, $CHCl_3$).

IR (KBr): 3419, 2807, 2770, 1495, 1448, 1312, 815, 746 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.58 (br s, 1 H, N*H*), 2.77–2.91 (m, 2 H, NHCHCH_2), 3.53 (dd, 1 H, *J* = 5.0, 9.6 Hz, NHC*H*CH_2), 3.91–4.06 [m, 9 H, NHCH(C_5H_4)Fe(C_5H_5), CH_2NHCHCH_2], 4.16–4.21 [m, 2 H, NHCH(C_5H_4)Fe(C_5H_5)], 6.88–6.93 (m, 1 H, CH_{arom}), 6.99–7.03 (m, 1 H, CH_{arom}), 7.05–7.12 (m, 2 H, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 37.2, 48.9, 52.8, 66.3, 66.8, 67.5, 67.7, 68.5, 93.0, 125.8, 126.0, 126.1, 129.2, 135.2, 136.1.

MS (EI): *m*/*z* (%) = 318 (22), 317 (M^+, 100), 316 (14), 315 (17), 314 (8), 313 (16), 252 (6), 251 (25), 250 (9), 249 (16), 248 (9), 222 (6), 213 (13), 194 (5), 186 (23), 165 (8), 131 (11), 130 (22), 121 (9), 56 (8).

Anal. Calcd for $C_{19}H_{19}FeN$: C, 71.94; N, 4.42; H, 6.04. Found: C, 72.10; N, 4.54; H, 5.89.

(3*S*)-3-Furan-2-yl-1,2,3,4-tetrahydroisoquinoline [(*S*)-6e]

According to the general procedure GP 5 (2*R*,3*S*)-**3e** (100 mg, 0.31 mmol) was reacted with BH_3·THF (6.2 mL, 6.2 mmol). After purification by column chromatography (Et_2O–hexanes, 1:1) (*S*)-**6e** (29 mg, 47%) was obtained as a colorless oil.

ee ≥99% (HPLC, Daicel OJ, *n*-heptane–*i*-PrOH, 95:5).

R_f = 0.1 (Et_2O–hexanes, 1:1); $[\alpha]_D^{23}$ = –36.9 (c = 1.02, $CHCl_3$).

^1H NMR (300 MHz, C_6D_6): δ = 1.38 (br s, 1 H, N*H*), 2.79–2.95 (m, 2 H, NHCHCH_2), 3.68–3.84 (m, 2 H, CH_2NH), 3.90 (dd, 1 H, *J* = 5.6, 8.1 Hz, NHC*H*CH_2), 6.03–6.06 (dt, 1 H, *J* = 0.8, 3.3 Hz, OC=C*H*), 6.10 (dd, 1 H, *J* = 1.8, 3.2 Hz, OCH=C*H*), 6.76–6.80 (m, 1 H, CH_{arom}), 6.88–6.94 (m, 1 H, CH_{arom}), 6.97–7.05 (m, 2 H, CH_{arom}), 7.11 (dd, 1 H, *J* = 0.8, 1.9 Hz, OC*H*=CH).

^{13}C NMR (75 MHz, C_6D_6): δ = 34.0, 48.1, 51.8, 105.2, 110.4, 126.0, 126.2, 126.3, 129.4, 134.4, 135.8, 141.5, 157.8.

All other analytical data correspond with those of the literature.[38]

(3*R*)-7-Methyl-3-ferrocenyl-1,2,3,4-tetrahydroisoquinoline [(*R*)-6f]

According to the general procedure GP 5 (2*S*,3*R*)-**3f** (172 mg, 0.37 mmol) was reacted with BH_3·THF (7.5 mL, 7.5 mmol). After purification by column chromatography (Et_2O + 1% Et_3N) (*R*)-**6f** (82 mg, 67%) was obtained as a orange-red solid.

ee ≥97% (HPLC, Daicel AD, *n*-heptane–*i*-PrOH, 90:10).

Mp 72 °C; R_f = 0.15 (Et_2O); $[\alpha]_D^{24}$ = +67.8 (c = 0.61, $CHCl_3$).

IR (KBr): 3447, 2918, 2900, 2826, 2798, 2772, 1501, 1449, 1426, 1412, 1353, 1313, 1297, 1236, 1127, 1105, 1052, 1038, 1012, 999, 837, 813, 782 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 1.58 (br s, 1 H, N*H*), 2.19 (s, 3 H, CH_3), 2.79–2.91 (m, 2 H, NHCHCH_2), 3.57 (dd, 1 H, *J* = 5.6, 8.9 Hz, NHC*H*CH_2), 3.93–4.09 [m, 9 H, NHCH(C_5H_4)Fe(C_5H_5), CH_2NH], 4.18–4.23 [m, 2 H, NHCH(C_5H_4)Fe(C_5H_5)], 6.73 (s, 1 H, CH_{arom}), 6.91–6.98 (m, 2 H, CH_{arom}).

^{13}C NMR (100 MHz, C_6D_6): δ = 21.1, 36.8, 48.9, 53.0, 66.4, 66.9, 67.5, 67.7, 68.5, 93.2, 126.7, 126.9, 129.1, 132.2, 134.8, 135.9.

MS (EI): *m*/*z* (%) = 332 (26), 331 (M^+, 100), 330 (14), 329 (12), 266 (8), 265 (29), 264 (10), 263 (15), 262 (6), 236 (7), 213 (29), 212 (5), 211 (5), 208 (6), 199 (8), 187 (6), 186 (36), 179 (5), 178 (5), 165 (5), 146 (6), 145 (15), 144 (31), 121 (14), 117 (5).

Anal. Calcd for $C_{20}H_{21}FeN$: C, 72.52; N, 4.23; H, 6.39. Found: C, 72.32; N, 4.21; H, 6.36.

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