Substituted Isoquinolines by Noyori Transfer Hydrogenation: Enantioselective Synthesis of Chiral Diamines Containing an Aniline Subunit

E. Vedejs*

University of Wisconsin, Madison, Wisconsin 53706

P. Trapencieris and E. Suna

Organic Synthesis Institute, Riga, Latvia LV 1006

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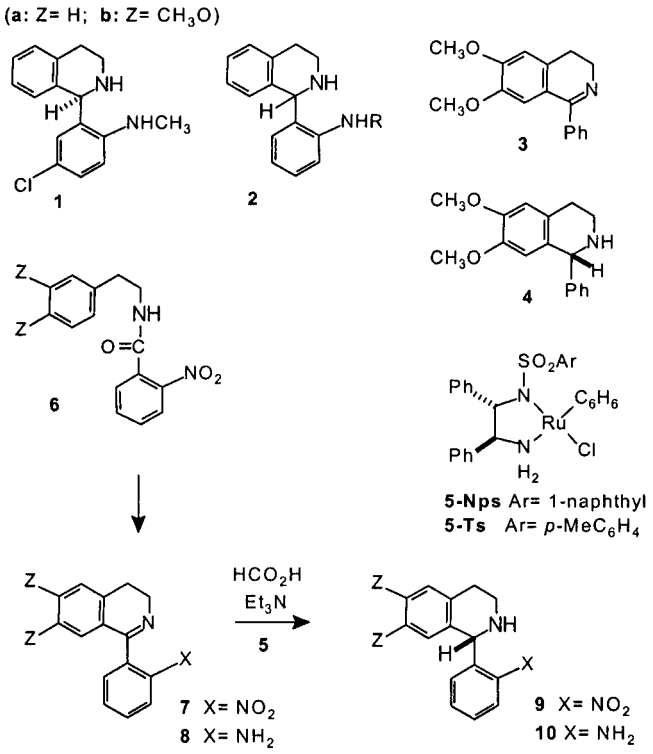
Transfer hydrogenation using the Noyori catalyst **5-Ts** is effective for the enantioselective hydrogenation of imines containing fully substituted nitrogen groups (**12** or **13**). Analogues such as **11c** could not be reduced in practical yield, apparently due to product inhibition of the catalyst. Asymmetric transfer hydrogenation of the aniline imine **8a** was possible, but required impractical purity levels for the substrate, and the nitro analogue **7** could not be reduced efficiently. The best results were obtained with the bromophenyl imine **20**. In the case of **20b**, the product **21b** was formed with 98.7% ee, and the material could be upgraded to >99% ee by crystallization of the hydrochloride salt. Reaction of **21b** with NH_3 or $MeNH_2$ in the presence of Cu/CuCl gave the chiral anilines **10b** or **23b**. The latter substance is comparable to the commercially available **1** as a chiral proton donor for amide enolates and provides access to the hitherto unavailable enantiomeric series.

As part of a study involving the use of chiral aniline **1** as an asymmetric proton donor, we have been interested in developing an efficient enantioselective synthesis of *o*-aminoarylisoquinolines **2**.[1] In particular, we hoped to prepare the unsubstituted analogue **2** with R = H. This substance should provide easy access to a variety of N-substituted analogues of **1**, chiral anilines that could be used to probe structural and pK_a effects in the asymmetric protonation of enolates. An efficient route to isoquinoline derivatives related to **2** has recently been described by Noyori et al. via the asymmetric transfer hydrogenation of imines such as **3**.[2] The reported conversion from **3** to **4** was catalyzed by the ruthenium complex **5-Nps** (Ar = 1-naphthyl) and proceeded in good yield and with promising enantioselectivity (84% ee). The corresponding process for our purposes would have to be performed with ortho-substituted imines **7** or **8** (X = NO_2 or NH_2) or with analogous imines where X might be a leaving group that can be converted into nitrogen functionality. Ideally, asymmetric hydrogenation would be performed with substrates having Z = H. However, Z = OCH_3 should not interfere in the intended asymmetric protonation applications using derivatives of **10b**, and this substitution pattern may be necessary for high enantioselectivity in the Noyori reductions. Thus, the dimethoxy series (**b** series; Z= CH_3O, Scheme 1) as well as the parent system (**a** series; Z = H) was selected for the initial attempts to prepare analogues of **1**.

Scheme 1



The most direct route to **10** would be via reduction of the imines **7** or **8**. The nitro imines **7** were easily prepared by standard Bischler−Napieralski cyclization from **6**,[3] and reduction with Fe/HCl gave the imino anilines **8a** and **8b** (Scheme 1; 68 and 86% yield, respectively). However, the product anilines were contaminated with an intensely yellow impurity that could not be removed by chromatography.[4] With impurity levels near 20%, transfer hydrogenation did not occur within 16 h at 20 °C. Repeated crystallizations reduced the amount of the contaminant to 2%, but with considerable material loss. When **8a** containing ca. 2% of the impurity was treated

(1) (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792.

(2) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. Hashiguchi, S.; Noyori, R. *Acc. Chem. Res.* **1997**, *30*, 97.

(3) Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A. J.; Gogerty, J. H.; Leslie, G. H.; Trapold, J. H. *J. Med. Chem.* **1968**, *11*, 777.

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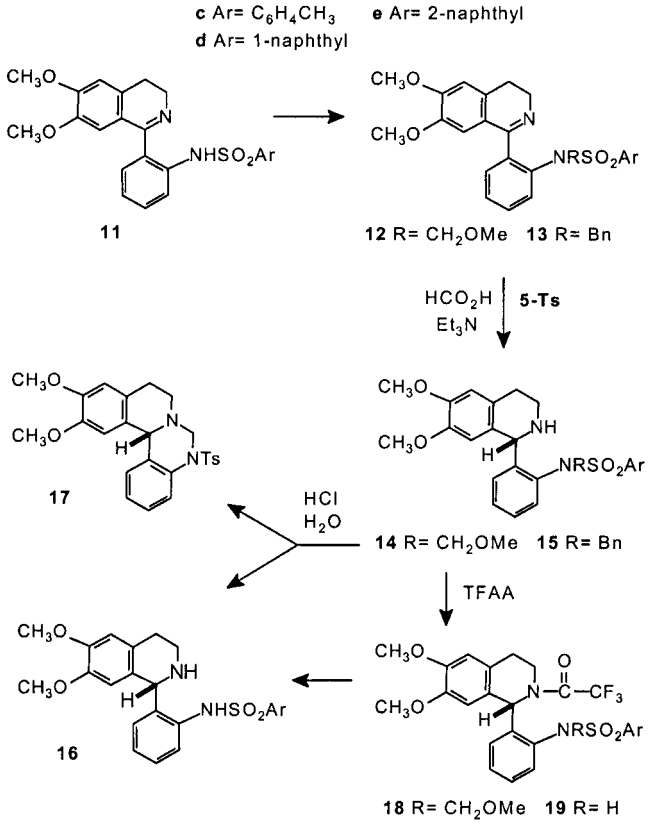
with 1 mol % of the catalyst **5-Nps** and HCO_2H/NEt_3, reduction did take place and the expected diamine **10a** was obtained in 75% yield and with 71% ee. In another attempt using a different batch of catalyst, the ee value mysteriously increased to 83% ee, and similar inconsistencies were encountered in attempts to hydrogenate **3**. No substantial difference between the two batches of **5-Nps** could be detected using NMR methods, but the limited solubility of both **5-Nps** and its precursor $(C_6H_6)_2$-$RuCl_2$[5] complicates catalyst assay using spectroscopy. We made no attempt to define the source of the problem in catalyst preparation because relatively consistent results were obtained with a modified Noyori catalyst **5-Ts** (Ar = MeC_6H_4).[6] This catalyst reduced purified **8a** (2% contaminant) in 66% yield (85% ee). However, if the starting aniline **8a** contained higher levels of the yellow contaminant, then conversion decreased, suggesting that the impurity inhibits the catalyst. Since the yellow contaminant was difficult to remove and the enantioselectivity was modest, attention was turned to alternative approaches as described below. Most of the subsequent studies were performed using **5-Ts** as the catalyst for asymmetric transfer hydrogenation.

One desirable option is to perform the asymmetric reduction at the nitro imine stage (**7**) in the hope that the nitro group might survive treatment with HCO_2H/Et_3N and catalyst **5-Ts**. Unfortunately, this variation also encountered poor conversion to products. At the 1 mol % catalyst loading level, **7a** was not reduced at a useful rate, while **7b** afforded ca. 20% of **9b** after 13 h. Increased conversion resulted using higher catalyst loading, but practical yields were not obtained. On the other hand, the enantioselectivity measured for the product **9b** was excellent (97.1% ee). This result did not solve the preparative problem, but high ee was encouraging because it indicated that the nature of the ortho substituent is important and might be used to control the asymmetric hydrogenation. Other ortho-substituted systems were therefore explored (Scheme 2). The initial focus was on the dimethoxy series, corresponding to the **b** series of Scheme 1, and the goal was to identify a dominant ortho substituent that would allow sufficient control over the asymmetric hydrogenation to afford good enantioselectivity with or without the methoxy substituents.

Conversion of **8b** into the corresponding *N*-tosyl derivative proceeded smoothly in pyridine with TsCl to give **11c** in 89% yield (Scheme 2). However, attempted asymmetric hydrogenation again was frustrated by poor conversion. Thus, **11c** gave no product within 16 h using 2 mol % of catalyst **5-Ts** and only 11% conversion after 72 h with 7.5 mol % of catalyst. As before, excellent ≥96% ee was obtained in the reduction step, but conversion remained problematic.

Scheme 2

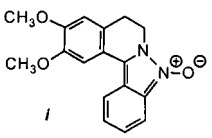


Since catalyst inhibition had been a recurring theme in the reductions, we suspected that the problem might be due to the sulfonamide N−H group. Blocking this site would minimize the risk that the product amino sulfonamide might act as a bidentate ligand for ruthenium. Accordingly, **11c** was converted into the *N*-methoxymethyl or *N*-benzyl derivatives **12c** and **13c**. The reductions were still rather slow and required 3−4 days using 6−7.5% of the catalyst **5** for 60−75% conversion to products **14c** or **15c**. In both cases, excellent enantioselectivity of 98% ee or better was obtained.

After considerable effort, **15c** could not be debenzylated without at least some (4−15%) racemization (palladium-catalyzed hydrogenolysis conditions). On the other hand, treatment of **14c** with dilute HCl produced the desired **16c** together with a byproduct (tentatively, **17**) that was resistant to hydrolysis. This problem could be avoided by converting the crude reduction product to the *N*-trifluoroacetamide **18c**, hydrolyzing the latter to **19c**, and cleaving the trifluoroacetyl group using K_2CO_3/H_2O−MeOH. The sequence succeeded to the extent that a family of potentially useful, chiral aniline derivatives **16c**−**e** having enhanced N−H acidity became available from the corresponding imines **12c**−**e** with high enantiomeric purity (>99% ee after crystallization). However, the number of steps necessitated by the problems with catalyst inhibition, as well as the complications with the protecting group chemistry, combined to make this approach relatively laborious.

One additional series of imine derivatives **20** (*o*-bromophenyl series) was examined, and this eventually provided the best route to diamines **10** (Scheme 3). Asymmetric hydrogenation of **20b** proceeded without any

(4) The yellow contaminant could not be separated well enough to give satisfactory analysis or spectra, but one small sample was obtained having a 3:2 ratio of oxygen/nitrogen according to elemental analysis, consistent with structure *i*, below. Analogous indazole *N*-oxides are reported as yellow solids: Reissert, A.; Lemmer, F. *Chem. Ber.* **1926**, *59*, 351. Behr, L. C. *J. Am. Chem. Soc.* **1954**, *76*, 3672. Behr, L. C.; Alley, E. G.; Levand, O. *J. Org. Chem.* **1962**, *27*, 65.

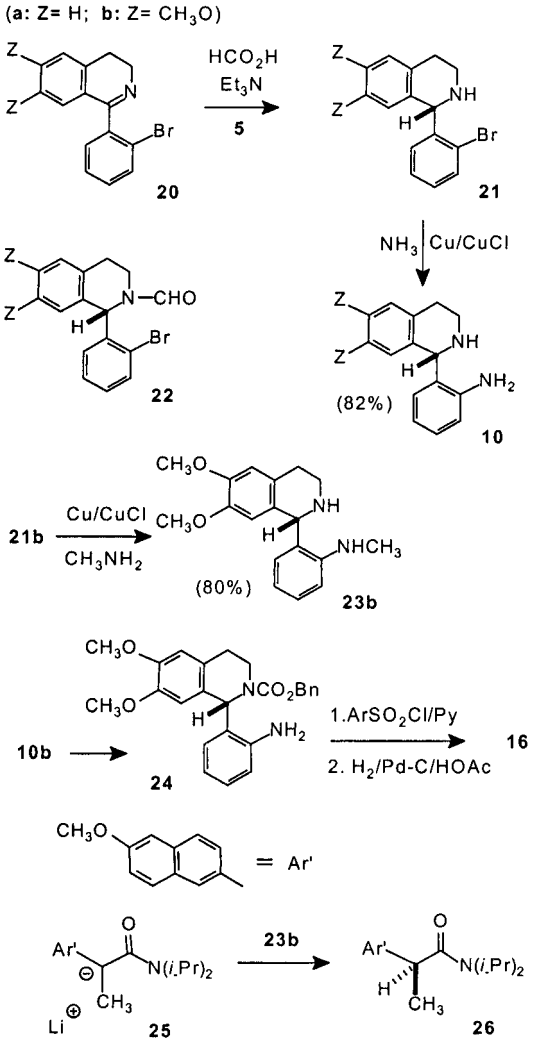


i

(5) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans. 1* **1974**, 233.

(6) Noyori, R.; Ikariya, T. Personal communication.

Scheme 3



of the complications encountered with the *o*-amino derivatives. Catalyst loading of 0.67 mol % gave **21b** with reasonable conversions of 67% and with excellent 98.7% ee. When the same conditions were tested with **20a**, the reaction was marginally slower and less selective (94% ee). However, practical results were realized in each case. Thus, the *o*-bromophenyl group provides sufficient control in the asymmetric hydrogenation step so that useful ee levels can be achieved with or without the methoxy substituents.

The asymmetric reductions could be performed as reported by Noyori et al,[2] but several variables deserve comment, starting with the procedure for catalyst preparation. The method is relatively simple, $(C_6H_6)_2RuCl_2$[5] + $H_2NCHPhCHPhNHSO_2Ar$; Et_3N/*i*-PrOH, reflux, but the catalyst is reported to decompose upon attempted purification. These properties caused some concern when one batch of **5-Nps** was found to give inferior enantioselectivities in some of our early attempts. However, the same batch of **5-Nps** catalyzed the transfer hydrogenation of **20a** or **20b** with excellent enantioselectivities (**20a**: 59% yield, 94% ee; **20b**: 71% yield, 98.3% ee). Both catalysts **5-Ts** and **5-Nps** are easy to store and to handle. Consistent results were obtained using a given batch of catalyst over a period of several weeks, so the hydrogenation of the best substrates (*o*-bromophenyl imines **20**) does not appear to be capricious.

Problems were also encountered with conversion of the imine substrate and yield of the products. Some of the early hydrogenations gave <25% conversion, but this difficulty was overcome by the simple expedient of venting the reaction vessel. Evidently, it is important to provide an exit for the gases (H_2 + CO_2) produced by decomposition of the HCO_2H/Et_3N reducing reagent as the hydrogenation proceeds. This version of catalyst inhibition is a minor problem compared to the examples discussed earlier where reduction products or impurities appear to act as catalyst inhibitors.

One complication was encountered to varying degrees in all of the hydrogenations, increasingly so for the slower reductions. This involved conversion of the product into the *N*-formyl derivative by the Et_3N/HCO_2H reagent. In the case of **20b**, use of 1 mol % of catalyst **5-Ts** resulted in 8% of **22b** at 92% conversion (84% of **21b**), and the amount of **22b** increased with time. In a similar experiment using 0.67 mol % catalyst, the reaction was slower (24 h vs 13 h) and **22b** was formed in 19% yield (97% conversion). Because of this problem, we were unable to obtain yields much above 70% in a number of experiments, including a preparative scale (18 g) hydrogenation of **20b**. However, the initially formed bromophenyl isoquinoline **21b** was conveniently isolated and purified as the hydrochloride salt, 72% from **20b** after crystallization (1.7 g scale; 62% yield on 18 g scale). When **21b** was released from the hydrochloride with aqueous base, >99% ee was measured for the upgraded material. Thus, the asymmetric hydrogenation and subsequent crystallization provides material with excellent enantiomeric purity and in reasonable yield.

With practical access to >99% enantiomerically pure **21b** established, the problem of replacing bromide by an amino group was investigated. This proved to be relatively easy by an adaptation of the method published in 1968 by Ott et al.[3] Thus, **21b** was treated with liquid NH_3 in the presence of copper powder and CuCl in a Parr reactor, 70 °C, for 5 days. The product **10b** was obtained in 82% yield after crystallization, and with 99% ee. In a similar process, **21b** reacted with CH_3NH_2/Cu/CuCl to afford **23b**, 80% isolated after crystallization, 99% ee.

The asymmetric hydrogenation−amination sequence provided sufficient **10b** to allow reinvestigation of the sulfonamide derivatives. After secondary amine nitrogen was protected as the Cbz derivative **25**, N-sulfonylation could be carried out without complications, and deprotection (H_2/Pd−C) gave sulfonamides **16c**−**e**. The absolute configuration of **16c** prepared starting from **20b** was the same as for the material derived from **12c**. Similarly, **10b** prepared by either route had the same configuration. The absolute configuration was confirmed by X-ray crystallography in the case of the crystalline *N*-formyl byproduct **22b** (anomalous dispersion method). Thus, all of the hydrogenations correspond to Noyori's model for asymmetric induction.[2]

Finally, the diamine **23b** was tested in the asymmetric protonation of the amide enolate **25**. The reaction proved somewhat more sensitive to temperature changes compared to the analogous process using **1**. However, addition of precooled **23b** to the enolate gave reproducible results, and this small modification of the usual procedure[1a] gave **26** with 88.8% ee. The corresponding experiment using the dechloro analogue of **1** results in

Table 1. Asymmetric Transfer Hydrogenation of Imines[a]

entry	imine	Z	X	cat. (mol %)	time (h)	yield (%)	ee (%)
1	**3**			**5-Ts** (0.5)	8	99[2]	84[2]
2	**7a**	H	NO_2	**5-Ts** (1)	13	<1	
3	**7b**	MeO	NO_2	**5-Ts** (1)	13	20	97.1
4	**8a**	H	NH_2	**5-Ts** (2)	16	66	85
5	**11c**	MeO	NHTs	**5-Ts** (2)[b]	16	<1	
6	**11c**	MeO	NHTs	**5-Ts** (7.5)[c]	72	11	96
7	**12c**	MeO	N(MOM)-Ts	**5-Ts** (7.5)[c]	84	58[d]	>99
8	**12d**	MeO	N(MOM-Ms[e]	**5-Ts** (7.5)[c]	84	53[d]	93[c]
9	**12e**	MeO	N(MOM)-(1-Nps)[f]	**5-Ts** (7.5)[c]	84	53[d]	97
10	**13c**	MeO	NBnTs	**5-Ts** (7.5)	72	76[g]	≥98[h]
11	**20a**	H	Br	**5-Ts** (1)	13	41	94
12	**20a**	H	Br	**5-Nps** (1)	13	59	94
13	**20b**	MeO	Br	**5-Ts** (0.67)	13	67	98.7
14	**20b**	MeO	Br	**5-Nps** (0.67)	13	71	98.3

[a] Unless indicated otherwise, all reactions were done in CH_2Cl_2 at rt, 0.4 M substrate, 6:1 ratio of Et_3N/HCO_2H azeotrope/substrate; conversion was established by HPLC analysis. [b] 30:1 ratio of Et_3N/HCO_2H azeotrope/substrate. [c] 55:1 ratio of Et_3N/HCO_2H azeotrope/substrate. [d] Isolated yield of purified material. [e] 1-Naphthylsulfonyl. [f] 2-Naphthylsulfonyl. [g] Overall yield of *N*-trifluoroacetamide **18** (R = Bn) from **13c**. [h] Assayed as the *N*-trifluoroacetamide **18** (R = Bn).

90% ee.[7] As expected from the configuration of **23b**, the major product is enantiomeric with **26** obtained using **1**. Since only the (*R*)-enantiomer **1** is commercially available, the Noyori reduction method described here provides access to the complementary series of asymmetric proton donors. The original literature method used in the synthesis of (*R*)-**1** involves a nonselective reduction step followed by resolution,[3] so a Noyori reduction approach using the enantiomer of catalyst **5** may be an effective alternative. Further studies are planned to test derivatives of **10a** and **10b** in asymmetric anion protonation and will be described in subsequent publications.

Conclusions

The Noyori reduction procedure affords excellent enantioselectivities with several of the ortho-substituted imines (Table 1).[2,8] High enantiomer excess was observed with ortho substituents of varying steric bulk and electronic properties, including *o*-Br, *o*-NO_2, and *o*-N(R)SO_2-Ar (Table 1, entries 3 and 6−15), so the exact source of the improvement over the parent system (entry 1) is not clear. However, a simple *o*-methyl substituent also improves enantioselectivity,[9] so the substituent effect could be steric in nature. If the ortho substituent is needed to favor a specific rotamer in one of the competing diastereomeric transition states for hydrogenation, then good ee might be expected with the diverse ortho substituents, but we cannot explain the subtle variations among the nitrogen substituents.

The principal limitation of the asymmetric hydrogenation procedure at the current level of development is in the sensitivity to product inhibition. Substrates chosen to minimize this problem (for example, **14**, **15**, **20**) could be reduced in acceptable yield, although some material was lost to N-formylation in all cases. However, this is a small complication in view of the convenience of using Et_3N/HCO_2H as the reducing agent. The Noyori procedure is relatively easy, and no special apparatus is required. In the case of **20b**, scale-up to 18 g was carried out with a 10% loss in yield, but without encountering other complications. While the method does not tolerate a broad range of ortho substituents, it works quite well with the versatile *o*-Br substrate.[10] Combined with the copper-catalyzed aminations,[11] this approach is currently the method of choice for the synthesis of structures related to **1**.

Experimental Section

General Methods. Column chromatography was performed using Acros silica gel (0.06−0.2 mm).

General Procedure for Asymmetric Transfer Hydrogenation (0.5 mmol Scale; Table 1). The 3,4-dihydroisoquinoline (0.5 mmol) and Ru catalyst **5** (see Table 1 for loading) were placed in a 2 mL vial fitted with a septum, outlet needle (important!), and stirring bar, and CH_2Cl_2 (1.0 mL, distilled from CaH_2 prior use) was added followed by the formic acid−triethylamine 5:2 azeotrope[12] (0.25 mL). The reaction mixture was stirred at room temperature (ca. 20 °C) for the apropriate time (see Table 1), and saturated Na_2CO_3 solution (0.25 mL) was carefully added (vigorous gas evolution!). After being stirred for 10 min, the mixture was partitioned between 8 mL of CH_2Cl_2 and 5 mL of Na_2CO_3 solution. The basic water layer was washed with 2 mL of CH_2Cl_2, the organic layers were combined, washed with water (3 × 2 mL) and brine, dried (Na_2SO_4), filtered, and evaporated (aspirator). The dark red-brown residue was filtered through a silica gel pad (column: 20 × 20 mm) using EtOAc (100 mL), solvent was removed (aspirator), and the residue was dried in vacuo (ca. 1 mmHg) over P_2O_5 for 12 h. After weighing, all the material was carefully dissolved in 5 mL of CH_2Cl_2, transferred into a 25 mL volumetric flask (with CH_2Cl_2 rinsing), and filled up to the mark with the appropriate HPLC eluent. An aliquot of 0.5 mL was transferred to another 10 or 25 mL volumetric flask and filled up to the mark with HPLC eluent. The resulting solution (usually 0.09−0.6 mg/mL, depending on HPLC separation conditions) was used for HPLC analysis to establish conversion and enantiomer excess.

HPLC Analysis and Characterization of Transfer Hydrogenation Reduction Products. *(S)*-1-(2-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9b): optical rotation (96.5% ee, HPLC/csp) $[\alpha]_D = -105.1$ ($c = 1.17$, $CHCl_3$); analytical TLC on silica gel, EtOAc, $R_f = 0.48$ (tailing). Pure material was obtained by crystallization from EtOAc/hexane: mp 144−145 °C; pale yellow crystals; IR (Nujol, cm^{-1}) 3313 NH, 1532 NO_2, 1367 NO_2; 200 MHz NMR ($CDCl_3$, ppm) δ 7.74−7.69 (1H, m) 7.38−7.22 (2H, m) 7.03−6.98 (1H, m) 6.53 (1H, s) 6.08 (1H, s) 5.43 (1H, s) 3.76 (3H, s) 3.54 (3H, s) 3.05−2.59 (4H, m) 2.49−2.00 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 150.1, 147.8, 147.1, 138.8, 132.1, 131.8, 128.2, 127.9, 127.7, 123.9, 111.3, 110.7, 55.8, 55.7, 55.3, 40.6, 29.0. Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.78; N, 8.91. Found: C, 64.96; H, 5.84; N, 8.84. HPLC assay for conversion: Symmetry

(7) Vedejs, E.; Kruger, A. W.; Suna, E. Manuscript in preparation.

(8) (a) For a recent review on asymmetric reduction of cyclic imines, see: Yurovskaya, M. A.; Karchava, A. V. *Tetrahedron: Asymmetry* **1998,** 3331. (b) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955. Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784. Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron: Asymmetry*, **1998**, *9*, 183. Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics*, **1998**, *17*, 3420.

(9) We thank Prof. Noyori for informing us of this result and for providing a sample of catalyst **5-Nps**.

(10) The chloro analogue of **20a** was reduced with promising ee (catalyst **5-Ts**: 66% yield, 91% ee; catalyst **5-Nps**: 56% yield, 86% ee), but the amine displacement was not attempted.

(11) The copper-catalyzed aminations give lower yields with larger *n*-alkylamines; for example, *N*,*N*-dimethylethylenediamine afforded 30% of the displacement product under the usual conditions.

(12) Prepared by slow addition of 96% HCOOH (Aldrich, 29.5 mL, 0.75 M) to a cooled neat NEt_3 (41.9 mL, 0.3M) and distillation of the resulting mixture in vacuo (aspirator, 15 mmHg, collected fractions bp: 91−92 °C, bath temperature 155−160 °C); see: Narita, K.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, *25*, 135.

C18, 15 cm × 3.9 mm i.d., mobile phase 50% acetonitrile/50% 0.2 M acetate buffer (pH = 5.0), flow rate 0.8 mL/min, detector UV 254 nm. Retention time: starting material **7b**, 3.6 min; product **9b**, 2.0 min. HPLC/csp: Daicel CHIRALCEL OD, 25 cm × 4.6 mm i.d., mobile phase 10% *i*-PrOH/90% Hex, flow rate 0.8 mL/min, detector UV 254 nm. Retention time: 13.9 min (*R* isomer), minor and 19.8 min (*S* isomer), major.

***(S)*-1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinoline (10a):** optical rotation (>99% ee, HPLC/csp) $[\alpha]_D = -42.5$ (c = 1.04, $CHCl_3$); analytical TLC on silica gel, 1:1 EtOAc/hexane, $R_f = 0.2$. Pure material was obtained by crystallization from EtOAc/hexane: mp 113−114 °C; colorless needles; molecular ion calcd for $C_{15}H_{16}N_2$ 224.13139, found m/e = 224.1312, error = 1 ppm; IR (KBr, cm^{-1}) 3388 NH, 3323 NH; 300 MHz NMR ($CDCl_3$, ppm) δ 7.18−6.98 (5H, m) 6.81 (1H, d, J = 7.8 Hz) 6.69 (1H, ddd, J = 7.5, 7.5, 1.5 Hz) 6.62 (1H, dd, J = 8.1, 1.2 Hz) 5.09 (1H, s) 4.49 (2H, br s) 3.31−3.22 (1H, m) 3.13−3.00 (2H, m) 2.84−2.75 (1H, m) 2.00 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 146.2, 137.5, 135.2, 131.2, 129.1, 128.6, 127.3, 127.0, 126.6, 126.0, 117.5, 116.9, 62.0, 43.1, 29.8. Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.31; H, 7.20; N, 12.49. Found: C, 80.09; H, 7.37; N, 12.43. HPLC/csp assay: Daicel CHIRALCEL OD, 25 cm × 4.6 mm i.d., mobile phase 5% EtOH/95% Hex/0.1% Et_2NH, flow rate 0.8 mL/min, detector UV 254 nm. Retention time: starting material **8a**, 12.3 min; product **10a**,-16.0 min (*R* isomer), minor and 16.9 min (*S* isomer), major.

***(S)*-1-(2-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (21a):** optical rotation (97% ee, HPLC/csp) $[\alpha]_D = -26.1$ (c = 1.15, $CHCl_3$); analytical TLC on silica gel, 1:3 EtOAc/hexane, $R_f = 0.24$; IR (Nujol, cm^{-1}) 3325 NH; 200 MHz NMR ($CDCl_3$, ppm) δ 7.60 (1H, dd, J = 7.4, 1.6 Hz) 7.25−6.97 (6H, m) 6.76 (1H, d, J = 7.4 Hz) 5.63 (1H, s) 3.24−2.81 (4H, m) 2.53 (1H, br s). ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 143.5, 136.9, 135.7, 132.8, 131.2, 129.1, 128.8, 128.0, 127.3, 126.4, 125.7, 124.6, 60.0, 41.1, 29.6. **Hydrochloride salt of 21a:** optical rotation (97% ee, HPLC/csp) $[\alpha]_D = -12.7$ (c = 1.19, H_2O). Pure material was obtained by crystallization from acetonitrile: mp 190 °C dec. Anal. Calcd for $C_{15}H_{15}BrClN$: C, 55.49; H, 4.67; N, 4.32. Found: C, 55.54; H, 4.63; N, 4.27. HPLC assay for conversion: Daicel CHIRALCEL OJ, 25 cm × 4.6 mm i.d., mobile phase 10% *i*-PrOH/90% Hex, flow rate 1.0 mL/min, detector UV 254 nm. Retention time: starting imine **20a**, 24.2 min; product **21a**, 6.4 min (*S* isomer), major and 7.6 min (*R* isomer), minor.

Preparative-Scale Synthesis of *(S)*-1-(2-Bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21b) by Transfer Hydrogenation. Imine **20b** (1.73 g, 5 mM) and Ru catalyst **5-Ts** (21.8 mg, 0.037 mM) were placed in a 15 mL Erlenmeyer flask fitted with a septum, outlet needle (important!), and magnetic stirring bar, and 10 mL of CH_2Cl_2 (distilled from CaH_2 prior use) was added, followed by 2.5 mL of HCOOH−NEt_3 5:2 azeotrope.[12] After the mixture was stirred at room temperature for 24 h, 10 mL of saturated Na_2CO_3 solution was added (caution: vigorous gas evolution!), and stirring was continued for an additional 5 min. The resulting mixture was diluted with 50 mL of CH_2Cl_2 and 30 mL of water, and the layers were separated. The organic phase was washed with saturated Na_2CO_3 solution (3 × 10 mL), 10 mL of water, and 10 mL of brine and dried (Na_2SO_4). After filtration and evaporation (aspirator), the residue was purified by flash chromatography (column: 200 × 35 mm) with 1:1 EtOAc/Hex, 100 mL of dead volume; collected fractions 14−19 (25 mL), then eluent changed to 3:1 EtOAc/Hex and an additional 450 mL collected to give 1.77 g of yellow-brown oil. The oil was dissolved in Et_2O (100 mL) and placed in a 200 mL round-bottom flask fitted with an efficient stirring bar, and HCl gas was passed over the solution until white flakes precipitated. The hygroscopic solid was quickly filtered, washed with dry Et_2O, dried in vacuo (aspirator), and recrystallized from diethyl ether−acetonitrile to give 1.41 g (72%) of white flakes of the hydrochloride salt of **21b** (hygroscopic!): mp 185 °C dec; $[\alpha]_D = -31.8$ (c = 1, H_2O); 360 MHz NMR ($CDCl_3$, ppm) δ 10.83 (1H, br s) 9.69 (1H, br s) 7.67 (1H, d, J = 7.6 Hz) 7.30−7.22 (3H, m) 6.64 (1H, s) 6.11 (1H, s) 5.99 (1H, s) 3.87 (3H, s) 3.63 (3H, s) 3.38−3.21 (3H, m) 3.07−2.99 (1H, m). Anal. Calcd for $C_{17}H_{19}BrClNO_2$: C, 53.07; H, 4.99; N, 3.64. Found: C, 53.07; H, 4.96; N, 3.76. A sample of the hydrochloride (100 mg) was dissolved in 10 mL water, basified with 1 N NaOH, and extracted with 3 × 5 mL portions of CH_2Cl_2. The combined organic extracts were washed with water (5 mL) and brine (5 mL) and dried (Na_2SO_4). After filtration and solvent removal (aspirator), 90 mg (99% yield) of colorless amine **21b** was obtained: optical rotation (99% ee, HPLC/csp) $[\alpha]_D = -62.4$ (c = 1, $CHCl_3$); analytical TLC on silica gel, EtOAc, $R_f = 0.55$; colorless oil; IR (neat, cm^{-1}) 3315 NH, 1263 (Ar)CO, 1230 (Ar)-CO; 360 MHz NMR ($CDCl_3$, ppm) δ 7.52 (1H, dd, J = 7.8, 1.3 Hz) 7.10 (1H, ddd, J = 7.4, 7.4, 1.3 Hz) 7.03 (1H, ddd, J = 7.6, 7.6, 1.9 Hz) 6.90 (1H, dd, J = 7.6, 1.9 Hz) 6.59 (1H, s) 6.21 (1H, s) 5.47 (1H, s) 3.83 (3H, s) 3.63 (3H, s) 3.05 (1H, ddd, J = 12.0, 6.8, 5.2 Hz) 2.99 (1H, td, J = 12.0, 5.7 Hz) 2.88−2.74 (2H, m) 2.18 (1H, br s); ^{13}C NMR (90 MHz, $CDCl_3$, ppm) δ 148.3, 147.7, 144.1, 133.1, 131.4, 129.0, 128.9, 128.3, 127.4, 124.7, 111.7, 111.1, 58.9, 55.31, 55.26, 39.9, 28.4.

Conversion of Aryl Bromide 21b to *(S)*-1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (10b). According to the method of Ott et al.,[3] a Parr pressure reactor (450 mL) was charged with **21b** (7.5 g, 19.5 mM), copper powder (Fluka, 488 mg, 7.7 mM), and copper(I) chloride (488 mg, 4.93 mM; washed with 1 N HCl, then carefully with water; dried in vacuo over P_2O_5, and stored in the dark), and 75 mL of liquid ammonia was carefully added. The reaction was heated and stirred at 70 °C (45 bar pressure) for 120 h and then cooled to room temperature, and ammonia was evaporated. The crystalline residue was partitioned between chloroform (100 mL) and water (100 mL). The dark blue water layer was washed with chloroform (2 × 20 mL), and the combined organic extracts were washed with water (3 × 30 mL) and brine and dried (Na_2SO_4). After filtration and solvent evaporation (aspirator), the residue was filtered through silica gel (column: 100 × 35 mm) using 800 mL of EtOAc to give crude product (5.27 g, 95% yield), which was recrystallized from EtOAc−hexane to yield 4.55 g (82%) of **10b**; analytical TLC on silica gel, EtOAc, $R_f = 0.2$; analytical HPLC/csp (Daicel CHIRACEL OD, 25 cm × 4.6 mm i.d.), mobile phase 20% EtOH/80% hexane, flow: 0.7 mL/min, retention time 13.0 min (*R* isomer), minor and 17.2 min (*S* isomer), major, ratio 99.5:0.5 (99% ee). Pure material was obtained by crystallization from EtOAc/hexane: mp 170−171 °C; colorless crystals; optical rotation $[\alpha]_D = +9.7$ (c = 1, $CHCl_3$); IR (Nujol, cm^{-1}) 3410 NH, 3320 NH, 1235 (Ar)CO; 360 MHz NMR ($CDCl_3$, ppm) δ 7.09 (1H, ddd, J = 7.7, 7.7, 1.6 Hz) 6.94 (1H, dd, J = 7.5, 1.6 Hz) 6.68 (1H, ddd, J = 7.5, 7.5, 1.1 Hz) 6.64 (1H, dd, J = 8.0, 1.1 Hz) 6.62 (1H, s) 6.33 (1H, s) 5.06 (1H, s) 4.54 (2H, br s) 3.86 (3H, s) 3.64 (3H, s) 3.22 (1H, dt, J = 12.0, 5.2 Hz) 3. 09−3.02 (1H, m) 2.98−2.90 (1H, m) 2.71 (1H, dt, J = 16.0, 4.6 Hz) 1.90 (1H, br s); ^{13}C NMR (90 MHz, $CDCl_3$, ppm) δ 147.7, 147.3, 146.2, 130.73, 130.69, 129.3, 128.4, 127.4, 127.3, 117.4, 116.6, 111.6, 110.0, 60.8, 55.8, 42.5, 29.2. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.79; H, 7.1; N, 9.85. Found: C, 71.76; H, 7.18; N, 9.87.

***(S)*-1-(2-Methylaminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (23b).** A 100 mL pressure reactor was charged with *(S)*-bromophenylisoquinoline hydrochloride **21b** (1.92 g, 4.99 mM), copper powder (Fluka, 126 mg, 1.99 mM) and copper(I) chloride (126 mg, 1.27 mM; washed with 1 N HCl, then carefully with water; dried in vacuo over P_2O_5, and stored in the dark), and 35 mL of liquid methylamine was added. The reaction was heated at 70 °C for 120 h, methylamine was evaporated, and workup was performed as described above for **10b**. Filtration through silica gel (column: 50 × 30 mm) using 300 mL of EtOAc gave a product that was recrystallized from EtOH to yield 1.19 g (80%) of **23b** as colorless crystals; analytical TLC on silica gel, EtOAc, R_f = 0.23−0.59 (tailing); analytical HPLC/csp (Daicel CHIRACEL OD, 25 cm × 4.6 mm i.d.), flow rate 1.0 mL/min, mobile phase 10% *i*-PrOH/90% hexane, retention time 13.6 min (*S* isomer), major and 17.3 min (*R* isomer), minor, ratio 99.5:0.5 (99% ee). Pure material was obtained by crystallization from ethanol: mp 96−97 °C; colorless crystals; $[\alpha]_D = +52.9$ (c = 1, $CHCl_3$); IR (Nujol, cm^{-1}) 3330 NH, 3320 NH, 1270 (Ar)CO; 300 MHz

NMR ($CDCl_3$, ppm) δ 7.21 (1H, ddd, J = 7.8, 7.8, 1.8 Hz) 6.88−6.85 (1H, m) 6.65 (1H, s) 6.62−6.60 (2H, m) 6.33 (1H, s) 5.04 (1H, s) 3.86 (3H, s) 3.63 (3H, s) 3.17 (1H, dt, J = 12.4, 5.6 Hz) 3.01 (1H, ddd, J = 12.4, 8.0, 5.0 Hz) 2.95−2.82 (1H, m) 2.75 (3H, s) 2.70 (1H, dt, J = 16.2, 5.0 Hz); ^{13}C NMR (75 MHz, DEPT, $CDCl_3$, ppm) δ 148.7, 147.6, 147.1, 130.4, 129.3, 128.6, 127.2, 126.7, 115.7, 111.4, 110.4, 110.0, 60.5, 55.8, 55.7, 42.2, 30.4, 29.1. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.44; H, 7.45; N, 9.39. Found: C, 72.50; H, 7.55; N, 9.33.

***(R)*-1-(2-Methylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (23a).** The title compound was prepared from **21a** as described for **23b**; HPLC/csp assay: Daicel CHIRALCEL OD, 25 cm × 4.6 mm i.d., mobile phase 5% *i*-PrOH/95% Hex, flow rate 0.8 mL/min, detector UV 254 nm. Retention time: **23a**,-10.4 min (*R* isomer), minor and 11.2 min (*S* isomer), major; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.44−0.19 (tailing). Pure material was obtained by crystallization from ethanol−water: mp 87−88 °C; colorless plates; optical rotation (99% ee, HPLC/csp) $[\alpha]_D$ = +5.2 (c = 1.17, $CHCl_3$); IR (Nujol, cm^{-1}) 3307 NH; 200 MHz NMR ($CDCl_3$, ppm) δ 7.23−7.13 (4H, m) 6.93 (1H, dd, J = 7.8, 1.8 Hz) 6.85−6.79 (1H, m) 6.68−6.61 (1H, m) 6.62 (1H, d, J = 7.8 Hz) 5.10 (1H, s) 3.31−2.96 (3H, m) 2.87−2.66 (1H, m) 2.71 (3H, s) 2.1−1.4 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 148.6, 137.5, 135.0, 130.7, 128.8, 128.6, 126.8, 126.4, 126.3, 125.7, 115.5, 110.5, 61.8, 42.7, 30.3, 29.6. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.62; H, 7.63; N, 11.76. Found: C, 79.70; H, 7.69; N, 11.61.

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Supporting Information Available: Preparation and characterization of imine starting materials for Table 1 and of the sulfonamide-derived reduction products; NMR spectra for asymmetric hydrogenation derived products described in the Experimental Section (**9b**, **10a**,**b**, **21a**,**b**, and **23b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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