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A Facile Synthesis of Vicinal Diamines Promoted by Low-Valent Niobium: Preparation of Chiral Octahydrobiisoquinolines and Their Application to Catalytic Asymmetric Synthesis

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An efficient homocoupling of imines to give vicinal diamines promoted by low-valent niobium, generated by treatment of $NbCl_5$ with zinc powder, is described. The desired products were obtained in good to excellent yields. Dihydroisoquinoline derivatives also gave the coupling products with good diastereoselectivities (D,L/*meso*). Optical resolution of the racemic octahydrobiisoquinolines was achieved and their complexes with Cu^I used in the catalytic asymmetric oxidative coupling of β-naphthols.

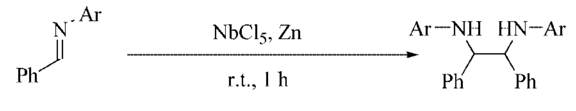
Introduction

Low-valent niobium reagents are well known to react with unsaturated bonds to give 1,2-dianion equivalents. Ever since Pedersen and co-workers reported the first successful results,[1–3] the chemistry of niobium has been an attractive area in organic synthesis due to its unique character. In fact, the generation of 1,2-dianion equivalents from imines,[1–3] carbonyl groups,[4–6] and alkynes[7–10] has been reported for useful chemical transformations, and a Nb–alkyne complex have been characterized.[11] We therefore became interested in the unique reactivity of 1,2-dianion equivalents and began to investigate imine coupling[12–15] using low-valent Nb reagents.[16]

Results and Discussion

Initially, we surveyed the role of a niobium reagent generated in situ in imine coupling. Although $[NbCl_3(DME)]$ is known to be a representative Nb^{III} reagent, its preparation and chemical stability are problematic. Therefore, we tried to generate a low-valent niobium reagent in situ by a reported procedure.[10] A solution of **1a** in THF was treated with low-valent niobium generated by the reduction of $NbCl_5$ with zinc powder, and gave the coupling product **2a** in 94% yield in a ratio of 1.5:1 (D,L/*meso*), although the polymerization of THF was a problem (Table 1, entry 1). This reaction was carried out under argon in a closed system to avoid cleavage of the newly formed carbon–carbon bonds promoted by a strong Lewis acid in the presence of trace amounts of molecular oxygen.[17] This homocoupling reaction also proceeded in CH_2Cl_2 and MeOH to give **2a** in yields of 85 and 97%, respectively (entries 2 and 3). Moreover, smaller amounts of $NbCl_5$ and Zn were sufficient to promote the reaction even at –78 °C in MeOH (entry 4). As expected, Nb^V and Zn powder are both essential in the homocoupling of **1a**: reaction in the absence of $NbCl_5$ or Zn powder gave either no reaction or *N*-(4-methoxyphenyl)benzylamine (74%), respectively (Scheme 1).

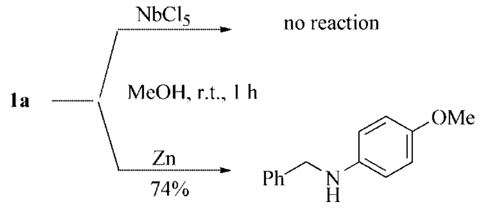
Table 1. Imine coupling promoted by low-valent Nb.



1a ($Ar = 4\text{-}MeOC_6H_4$) **2a**

Entry	Solvent	Nb (equiv.)	Zn (equiv.)	Yield of **1a** (%)	*dl*/*meso*
1	THF	2.4	6.0	94	1.5:1
2	CH_2Cl_2	2.4	6.0	85	2.0:1
3	MeOH	2.4	6.0	97	2.5:1
4	MeOH[a]	1.0	2.0	100	1.2:1

[a] The reaction was carried out at –78 °C.



Scheme 1. The reaction of **1a** without $NbCl_5$ or Zn powder.

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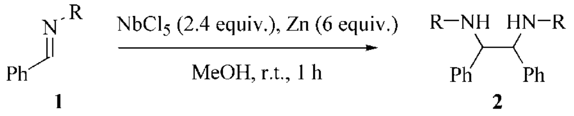
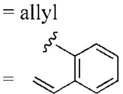
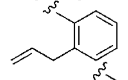
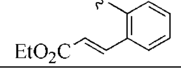
Next, we examined the reaction of substrates **1b–e**, which contain unsaturated bonds around the reaction center, under optimized conditions. As shown in Table 2, all of them were converted into the corresponding diamines **2b–e** in good yields. These results suggest that the reaction proceeds via a 1,2-dianion species rather than a radical process.

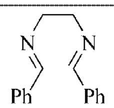
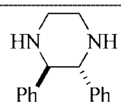
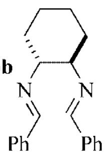
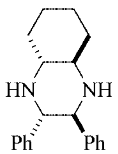
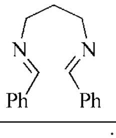
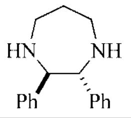
Table 2. *ortho*-Substituent effect.



Entry		Substrate	Yield of **2** (%)	*dl*/*meso*
1	**1b**	R = allyl	**2b**: 65	1.3:1
2	**1c**	R = 	**2c**: 83	1.5:1
3	**1d**	R = 	**2d**: 74	1.6:1
4	**1e**	R = 	**2e**: 52	1.5:1

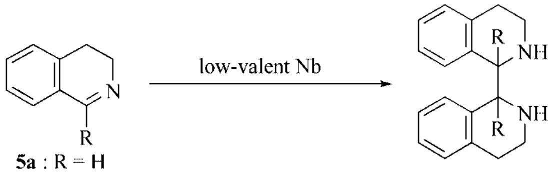
Intramolecular diamine coupling with **3** was also investigated. For example, **3a** was quantitatively transformed into the corresponding piperazine **4a** as a single isomer (Table 3, entry 1).[18] A bicyclic piperazine derivative was also obtained from **3b** in 98% yield (Table 3, entry 2).[19] However, attempts to obtain a seven-membered ring were unsuccessful and resulted in oligomerization (Table 3, entry 3).

Table 3. Intramolecular diamine coupling using low-valent Nb.[a]

Entry[a]		Substrate		Product	Yield (%)
1	**3a**		**4a**		100
2	**3b**		**4b**		98
3	**3c**		**4c**		0

[a] All reactions were carried out in the presence of NbCl$_5$ (1.2 equiv.) and Zn (3.0 equiv.) in MeOH at room temp. for 1 h.

Next, we turned to the Nb-mediated synthesis of octahydrobiisoquinoline (**6**) from **5** (Scheme 2).[20,21] Although **6** and its derivatives are expected to be biologically important molecules, useful ligands, or nucleophilic catalysts, only a few examples of their use in organic synthesis have been reported. A few methods for the preparation of **6a** by homocoupling of imines are known,[22,23] and excellent results for the diastereoselective synthesis of **6a** have been reported.[24] On the other hand, only one example of the synthesis of **6b** has been reported, and this homocoupling reaction, which uses Al(Hg) as a reducing agent, gives only a 9% yield of the required product together with the *meso* product in 34% yield.[25]



5a : R = H
5b : R = Me

6a: R = H
6b: R = Me

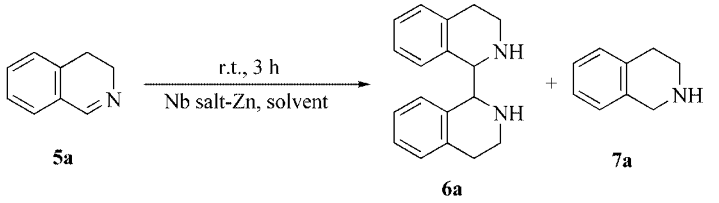
Scheme 2. Homocoupling of dihydroisoquinolines.

We initially surveyed the reaction conditions that would predominantly promote the desired homocoupling. Although the optimized conditions (MeOH, room temp., 3 h) for **5a** allowed the reaction to proceed, the undesired reduction to tetrahydroisoquinoline **7a** competed with the coupling to give adduct **6a** (D,L/*meso* = 1:1). On the other hand, direct use of Nb^{III} gave better results regarding the diastereoselectivity of **6a** (Table 4, entry 2), although a problem of reproducibility was observed. Finally, we succeeded in the development of a D,L-selective coupling with the generation of low-valent Nb in situ in DME/THF, as shown in entry 3. After washing the crude mixture with hexane/AcOEt (8:1), racemic **6a** was successfully isolated in 50% yield. These results are summarized in Table 4.

The optical resolution of (±)-**6a** was then investigated (Scheme 3). After a survey of chiral acids, (D)-CSA was found to be the most effective, and the diastereomerically pure salt of (+)-**6a** was obtained as a white, crystalline solid in 29% yield. The optical purity (>99% *ee*) was determined by HPLC analysis using a chiral column after conversion into the free base. Treatment of the resulting mother liquor with base, followed by salt formation with (L)-CSA, gave the optically pure salt of (–)-**6a** (>99% *ee*) in 31% yield. The absolute configuration of (+)-**6a** was determined to be (1*S*,1′*S*) by X-ray crystallographic analysis after transformation of (+)-**6a** into the corresponding dibenzamide **8** (Scheme 4). Its structure is shown in Figure 1.

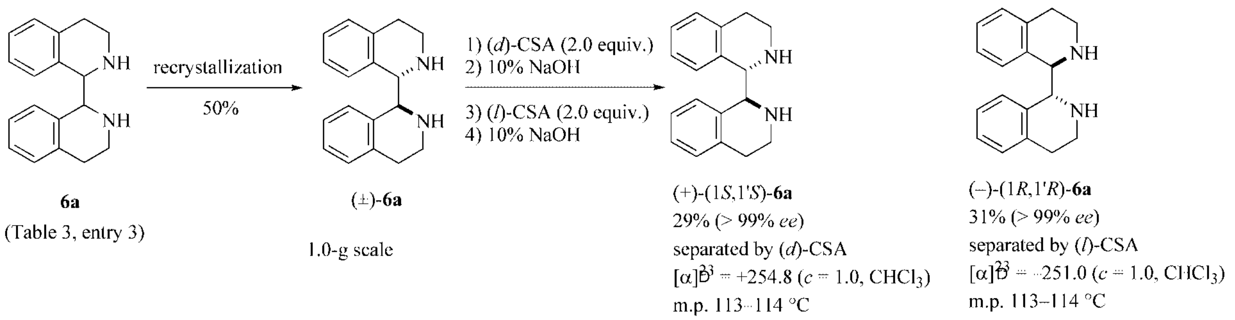
On the other hand, (±)-**6b** was also successfully prepared by the modified procedure outlined in Scheme 5. Treatment of **5b**[15] with NbCl$_5$/Zn in DME/THF (1:10) at room temp. gave **6b** in 89% yield as a 1:1 mixture of diastereomers along with **7b** (11% yield), as determined by ^{1}H NMR analysis. Racemic **6b** was isolated by formation of a salt with (D)-CSA, and subsequent treatment with base gave free (±)-**6b** in 41% yield. To the best of our knowledge, this is the most efficient methodology for the preparation of (±)-**6b**. Optical resolution of (±)-**6b** was achieved as a salt of (*S*)-BNHP (1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) to give (–)-**6b** in 15% yield with greater than 99% *ee*. Its enantiomer, (+)-**6b**, was isolated from the mother liquor in 24% yield and 98% *ee* by treatment with 10% NaOH fol-

Table 4. Synthesis of **6a**.

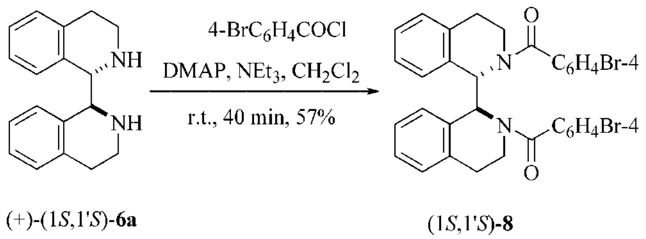


Entry	Solvent	Nb salt (equiv.)	Zn (equiv.)	*dl*-**6a**/*meso*-**6a**/**7a**[a]		
1	MeOH	$NbCl_5$ (2.4)	6.0	1	1	0.5
2	THF	$NbCl_3$ (DME) (2.4)	none	6~14	1	0.2
3 [b]	DME-THF (1:10)	$NbCl_5$ (2.4)	2.4	4.1[c]	1	0.6

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] 2.0 g of **5a**. [c] The average of four runs is 4.8:1 (D,L/*meso*).



Scheme 3. Isolation and optical resolution of **6a**.



Scheme 4. Determination of the absolute stereochemistry of **6a**.

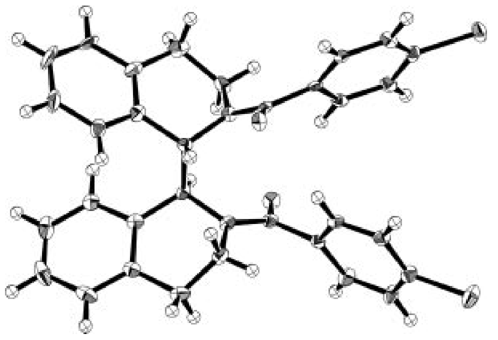
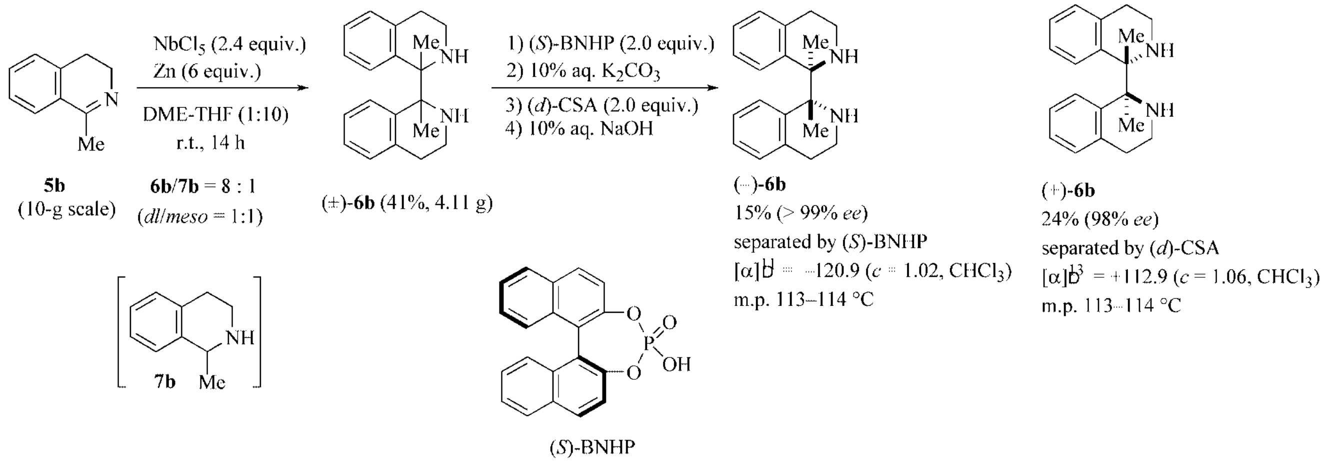


Figure 1. ORTEP diagram showing the X-ray structure of (1*S*,1*S*′)-**8**.

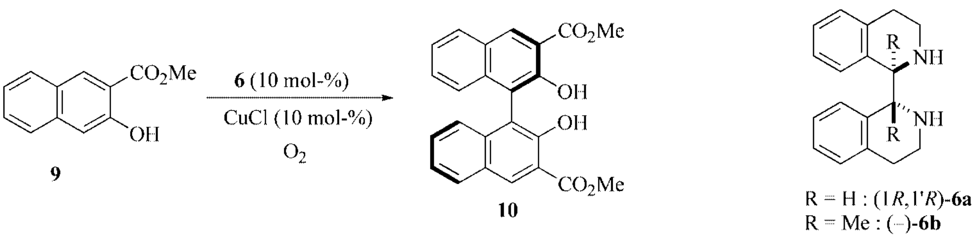
lowed by formation of the salt using (D)-CSA. Although the absolute configuration of **6b** has not yet been determined, we tentatively assigned the configurations, as shown in Scheme 5, by comparing the signs of optical rotation to those in **6a**.

With these two chiral diamines in hand, we next planned to investigate their utility as chiral ligands. Catalytic asymmetric oxidative coupling of β-naphthols is known to be one of the most efficient processes for obtaining chiral binaphthol derivatives, which are widely used as chiral ligands and auxiliaries. In their asymmetric synthesis, some chiral diamine complexes with Cu$^{\mathrm{I}}$ have been reported to play important roles in enantioselectivity.[26–28] First, the coupling reaction of β-naphthol-2-carboxylate (**9**) was investigated under various conditions. The reaction of CuCl with (–)-**6a** proceeded smoothly in various solvents under an oxygen atmosphere, but the yields were poor (Table 5, entries 1–4). Acetonitrile was found to be the best solvent, and gave the corresponding coupling product in 66% yield with 28% *ee* (entry 4). Product **10** was obtained with 48% *ee* when the reaction was conducted at 0 °C. On the other hand, the reaction with (–)-**6b**, which possesses methyl groups at the ring junction, gave **10** in 21% yield with 31% *ee* (entry 6). The absolute configuration of **10** was determined by comparing its $[a]_D$ value and retention time in HPLC analysis to data in the literature.[27] These results are summarized in Table 5.



Scheme 5. Synthesis, isolation, and optical resolution of **6b**.

Table 5. Catalytic asymmetric oxidative coupling of **9**.



Entry	Diamine	Solvent	Temp [°C]	Time [h]	Yield [%]	*ee* [%]
1	(1*R*,1'*R*)-**6a**	CH$_2$Cl$_2$	r.t.	24	73	16
2	(1*R*,1'*R*)-**6a**	MeOH	r.t.	27	100	6
3	(1*R*,1'*R*)-**6a**	Et$_2$O	r.t.	92	15	9
4	(1*R*,1'*R*)-**6a**	CH$_3$CN	r.t.	48	66	28
5	(1*R*,1'*R*)-**6a**	CH$_3$CN	0	48	60	48
6	(−)-**6b**	CH$_3$CN	0	21	21	31

Conclusions

In summary, we have developed an Nb-promoted imine-coupling reaction that gives the desired products in good to excellent yields. Moreover, the practical preparation and optical resolution of octahydrobiisoquinolines **6a** and **6b** have also been successful, and their application to the catalytic asymmetric synthesis has been demonstrated. The further application of these unique chiral diamines in organic synthesis is presently under investigation.

Experimental Section

General Remarks: NbCl$_5$ was purchased from Aldrich and used as received. All reactions were performed with dry solvents and reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25-mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel (Fuji Silysia, PSQ-60B). IR spectra were recorded on a JASCO FT/IR-230 Fourier transform spectrophotometer. NMR spectra were recorded on a JEOL-JMN-Alpha-400 spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, and calibrated relative to the residual undeuterated solvent as an internal reference. Mass spectra were measured with a JEOL JMS-AX500 (for LR-MS) and JEOL JMS-HX110 (for HR-MS).

General Procedure for Homocoupling of Imines. Synthesis of 2a: (Table 1, Entry 3) Zinc powder (47 mg, 0.72 mmol) was added to a suspension of NbCl$_5$ (78 mg, 0.29 mmol) in MeOH (2.4 mL) under argon. After stirring the mixture for 30 min, **1a** (50 mg, 0.24 mmol) was added at room temperature and the mixture was stirred for an additional hour. The reaction was quenched with 10% NaOH (5 mL) and extracted three times with AcOEt (15 mL). The combined organic layers were washed with brine and dried with Na$_2$SO$_4$. After removal of the organic solvent in vacuo, flash column chromatography on silica gel (hexane/AcOEt, 13:1) gave the desired product **2a** (49 mg, 0.116 mmol, 97%) as a yellow, amorphous solid. Diastereoselectivity was determined by ^{1}H NMR analysis. **2a**: CAS registration nos. (D,L): 35605-52-8; *meso*: 35583-32-5.

***N*,*N'*-Diallyl-1,2-diphenyl-1,2-ethylenediamine (2b) [CAS reg. nos. (D,L): 219517-95-0; *meso*: 219517-92-7] and 1,2-Diphenyl-*N*,*N'*-bis(2-vinylphenyl)-1,2-ethylenediamine (2c):** IR (KBr): $\tilde{\nu}$ = 3353, 3030, 2909, 1600, 1498, 1451, 1311, 748, 702 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 4.67 (s, 1.5/2.5 × 2 H), 4.75 (br, 2 H), 4.98 (d, J = 2.5 Hz, 1.0/1.5 × 2 H), 5.33 (d, J = 12.0 Hz, 2 H), 5.59 (dd, J = 17.4, 2.0 Hz, 1.5/2.5 × 2 H), 5.60 (dd, J = 17.4, 2.0 Hz, 1.0/2.5 × 2 H), 6.32 (d, J = 7.6 Hz, 1.5/2.5 × 2 H), 6.35 (d, J = 8.0 Hz, 1.0/2.5×2 H), 6.66 (t, *J* = 7.4 Hz, 2 H), 6.76 (dd, *J* = 16.6, 11.0 Hz, 2 H), 6.92–6.98 (m, 4 H), 7.17–7.26 (m, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 62.5, 63.8, 112.5, 112.6, 116.8, 116.9, 117.8, 118.0, 124.8, 125.3, 127.3, 127.4, 127.5, 127.7, 128.3, 128.5, 128.6, 128.7, 132.7, 132.8, 138.2, 139.7, 143.5, 143.9 ppm. LRMS (FAB): *m*/*z* = 417 $[M + H]^+$. HRMS (FAB): *m*/*z* calcd. for $C_{30}H_{29}N_2$ 417.2331; found 417.2305.

***N*,*N'*-Bis(2-allylphenyl)-1,2-diphenyl-1,2-ethylenediamine (2d):** IR (neat): $\tilde{\nu}$ = 3414, 3062, 2911, 1603, 1584, 1504, 1452, 1314, 916, 747, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.27 (d, *J* = 6.4 Hz, 1.6/2.6×4 H), 3.31–3.33 (m, 1.0/2.6×4 H), 4.55 (br. s), 4.70 (m, 2 H), 4.96–5.06 (m, 4 H), 5.87–5.96 (m, 2 H), 6.30 (dd, *J* = 1.2, 8.0 Hz, 1.6/2.6×2 H), 6.34 (dd, *J* = 0.8, 8.0 Hz, 1.0/2.6×2 H), 6.60–6.65 (m, 2 H), 6.89–7.04 (m, 6 H), 7.18–7.34 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 36.4, 36.7, 62.1, 63.4, 111.9, 112.3, 116.4, 116.4, 117.4, 117.7, 123.9, 124.5, 127.3, 127.4, 127.5, 127.5, 127.6, 128.2, 128.5, 129.7, 130.0, 135.8, 135.8, 138.4, 139.8, 144.5, 144.8 ppm. LRMS (FAB): *m*/*z* = 445 $[M + H]^+$. HRMS (FAB): *m*/*z* calcd. for $C_{32}H_{33}N_2$ 445.2644; found 445.2652.

Ethyl 3-{2-[2-(2-Ethoxycarbonylvinyl)phenylamino]-1,2-diphenylethylaminophenyl}acrylate (2e): IR (neat): $\tilde{\nu}$ = 3391, 3030, 2980, 1713, 1624, 1602, 1505, 1454, 1316, 1265, 1174, 701, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.30–1.34 (m, 6 H), 4.22–4.29 (m, 4 H), 4.76 (s, 1.5/2.5×2 H), 4.83 (br), 4.94 (s, 1.0/2.5×2 H), 6.31–6.40 (m, 4 H), 6.68 (t, *J* = 7.6 Hz, 2 H), 7.01–7.05 (m, 4 H), 7.20–7.37 (m, 14 H), 7.82 (d, *J* = 16.0 Hz, 1.5/2.5×2 H), 7.84 (d, *J* = 16.0 Hz, 1.0/2.5×2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 14.3, 60.4, 60.4, 62.8, 63.3, 113.3, 113.5, 118.2, 118.3, 119.2, 119.4, 121.0, 121.4, 127.3, 127.3, 128.0, 128.4, 128.6, 128.7, 128.8, 131.0, 131.1, 137.8, 138.7, 140.0, 144.8, 145.1, 166.9, 167.0 ppm. LRMS (FAB): *m*/*z* = 561 $[M + H]^+$. HRMS (FAB): *m*/*z* calcd. for $C_{36}H_{37}N_2O_4$ 561.2753; found 561.2721.

2,3-Diphenyldecahydroquinoxaline (4b): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39–1.41 (m, 4 H), 1.71–1.78 (m, 6 H), 2.61 (m, 2 H), 3.82 (s, 2 H), 7.10 (s, 10 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.9, 31.8, 61.5, 68.5, 127.1, 127.8, 128.0, 141.4 ppm. $[\alpha]_D^{13}$ = –71.7 (*c* = 0.87, $CHCl_3$). Reg. no. 169532-34-7.

Synthesis of (±)-1,2,3,4,1′,2′,3′,4′-Octahydro-1,1′-biisoquinoline (6a): Zinc powder (1.5 g, 22.8 mmol) was added, at 0 °C, to a suspension of $NbCl_5$ (6.2 g, 15.2 mmol) in DME (15 mL). After stirring this mixture for 30 min, it was diluted with THF (115 mL) and a THF solution of **5a** (2.0 g/20 mL) was added. Stirring was continued for an additional 3 h at room temp. The reaction was quenched with 10% aq. NaOH (50 mL) at 0 °C, and the mixture was filtered through a celite pad. The filtrate was separated and the aqueous layer was extracted three times with AcOEt (50 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvent in vacuo, the residue was treated with a mixture of hexane and AcOEt (8:1) to give (±)-**6a** (1.0 g, 50%) as crystals.

Optical Resolution of 6a: (D)-CSA (4.66 g, 20 mmol) was added to a solution of (±)–**6a** (2.65 g, 10 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred for 30 min at room temp. After removal of the solvent in vacuo, the resulting crude product was recrystallized from iPr_2O/EtOH (3 times) to give the salt as a white, crystalline solid (2.2 g). This was dissolved in H_2O/MeOH/Et_2O (10:1:10, 50 mL), neutralized by the addition of aq. 10% NaOH (60 mL) at 0 °C, and the free amine was extracted three times with AcOEt (20 mL,). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give (1*S*,1′*S*)-**6a** as a white solid (775 mg, 29%, >99% *ee*). The organic solvent was removed from the mother liquor, and the residue was dissolved in H_2O/MeOH/Et_2O (10:1:10, 30 mL) and treated with aq. 10% NaOH (60 mL) at 0 °C. After stirring the mixture for 30 min, it was extracted three times with AcOEt (20 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give (1*R*,1′*R*)-**6a** as a yellow solid (1.83 g, 69%, 40% *ee*). (L)–CSA was added, at room temp., (3.22 g, 13.8 mmol) to a solution of the resulting solid in CH_2Cl_2 (14 mL) and the mixture was stirred for 30 min. The solvent was evaporated to give a solid, which was recrystallized three times from iPr_2O/EtOH. The resulting white solid (2.3 g) was dissolved in H_2O/MeOH(Et_2O (10:1:10, 30 mL) and treated with 10% aq. NaOH (60 mL) at 0 °C. The mixture was extracted three times with AcOEt (20 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$ to give (1*R*,1′*R*)-**6a** as a colorless solid (810 mg, 31%, >99% *ee*). IR (KBr): $\tilde{\nu}$ = 3284, 3013, 2929, 1495, 1456, 1428, 1125, 865, 762, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.60 (d, *J* = 15.2 Hz, 2 H), 2.80 (dt, *J* = 3.2, 11.5 Hz, 2 H), 2.88–2.96 (m, 2 H), 3.18 (ddd, *J* = 2.4, 5.2, 11.5 Hz, 2 H), 4.68 (s, 2 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 7.15 (t, *J* = 7.2 Hz, 2 H), 7.21 (t, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.4, 42.8, 60.1, 125.1, 126.0, 126.2, 129.3, 136.6, 137.3 ppm. M.p. 113–114 °C; (1*S*,1′*S*): $[\alpha]_D^{22}$ = +254.8 (*c* = 1.07, $CHCl_3$) >99% *ee*; (1*R*,1′*R*): $[\alpha]_D^{22}$ = –251.0 (*c* = 1.02, $CHCl_3$) >99% *ee*; LRMS (FAB): *m*/*z* = 265 $[M + H]^+$. HRMS (FAB): *m*/*z* calcd. for $C_{18}H_{21}N_2$ 265.1705; found 265.1700. HPLC conditions: Daicel Chiralcel OD, hexane/*i*PrOH (9:1), flow rate = 0.5 mL min^{-1}, retention time: 17.7 (1*S*,1′*S*), 27.5 min (1*R*,1′*R*).

1,1′-Dimethyl-2,3,4,2′,3′,4′-hexahydro-1,1′-biisoquinoline (6b): DME (68 mL) was slowly added at –40 °C to $NbCl_5$ (22.3 g, 82.6 mmol) in a round-bottomed flask. Zinc powder (13.5 g, 207 mmol) was then slowly added at –40 °C and the mixture was stirred for a few minutes until the solution turned dark red. The mixture was stirred for 30 min at room temp. After addition of THF (600 mL) at –40 °C, the mixture was stirred for 3 h at room temp. and a THF solution (20 mL) of **5b** (10 g, 68.9 mmol) was added. The mixture was stirred for an additional 14 h. The reaction was then quenched with aq. 10% NaOH and the resulting mixture was filtered though a celite pad. The filtrate was extracted three times with AcOEt (150 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The resulting crude solid was dissolved in CH_2Cl_2 (100 mL), treated with (D)-CSA (16 g, 68.9 mmol), and the mixture was stirred for 30 min. The solvent was then removed to give a solid which was suspended in AcOEt (200 mL) and then filtered. The resulting solid was washed with AcOEt and dissolved in AcOEt/MeOH/H_2O (10:1:10, 200 mL) and 10% aq. NaOH (200 mL). The mixture was extracted three times with AcOEt (50 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated to give (±)-**6b** as a yellow solid (4.11 g, 41%).

Optical Resolution of (±)-6b: (*S*)-BNHP (1.77 g, 5.0 mmol) was added to a solution of (±)-**6b** (736 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) and MeOH (3.5 mL), and the mixture was stirred for 30 min at room temp. After removal of the solvent, recrystallization of the crude product from EtOH gave a white solid. Finally, recrystallization of the solid from EtOH gave a colorless solid (920 mg). The resulting solid was dissolved in 10% aq. K_2CO_3 (10 mL) and the mixture was extracted three times with AcOEt (10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. Purification by column chromatography on basic alumina (hexane/AcOEt, 1:1) gave (–)-**6b** as a colorless solid (109 mg, 15%, >99% *ee*). The mother liquor was treated with 10% aq. K_2CO_3 (30 mL) and AcOEt (10 mL), and the mixture was stirred for 1 h. After extraction three times with AcOEt (20 mL), the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give a yellow solid with the mixture of BNHP (554 mg, <75%, 49% *ee*). (D)-CSA (885 mg, 3.8 mmol) was added to a solution of the resulting yellow solid in CH_2Cl_2 (19 mL) and the mixture was stirred for 30 min. After removal of the solvent in vacuo, the resulting solid was washed with AcOEt and the mother liquor was treated with 10% aq. NaOH (30 mL). The mixture was extracted three times with AcOEt (15 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on basic alumina (hexane/AcOEt, 1:1) gave (+)-**6b** as a yellow solid (180 mg, 24%, 98% *ee*). IR (KBr): $\tilde{\nu}$ = 2990, 2948, 2900, 2827, 1490, 1457, 1148, 765, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.66 (s, 6 H), 1.90 (br. s, 2 H), 2.44–2.49 (m, 2 H), 2.86–2.94 (m, 4 H), 3.10–3.15 (m, 2 H), 6.86 (d, J = 7.2 Hz, 2 H), 6.95–7.03 (m, 4 H), 7.86 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.7, 31.7, 40.0, 63.5, 124.6, 125.4, 128.2, 128.5, 137.0, 141.5 ppm. M.p. 115–116 °C. $[\alpha]_D^{11}$ = –120.9 (c = 1.02, $CHCl_3$) >99% *ee* (1*R*,1′*R*), $[\alpha]_D^{13}$ = +112.9 (c = 1.06, $CHCl_3$) 98% *ee* (1*S*,1′*S*). LRMS (FAB): m/z = 293 $[M + H]^+$. HRMS (FAB): m/z calcd. for $C_{20}H_{25}N_2$ 293.2018; found 293.2004. HPLC conditions: Daicel Chiralcel OD-H, 0.1% Et_2NH in hexane/*i*PrOH (99:1), flow rate: 0.5 mL min^{-1}, retention time: 13.4 min for (–)-form, 14.2 min for (+)-form.

[*N*,*N*′-(4-Bromobenzoyl)-1,2,3,4,1′,2′,3′,4′-octahydro-1,1′-biisoquinolin-2-yl]-4-bromophenylmethanone (8): NEt_3 (79 μL, 0.57 mmol), DMAP (7 mg, 0.05 mmol), and *p*-bromobenzoyl chloride (91.8 mg, 0.42 mmol) were added, at room temp., to a solution of (+)-**6a** (50 mg, 0.19 mmol) in CH_2Cl_2 (3.8 mL) and the reaction mixture was stirred for 40 min. The reaction was quenched by the addition of sat. $NaHCO_3$ (3 mL) and the mixture was extracted three times with AcOEt (10 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After removal of the solvent in vacuo, the resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 8:1) to give **8** as a colorless solid (68.3 mg, 57%). M.p. 221–222 °C (EtOAc). IR (KBr): $\tilde{\nu}$ = 1634, 1429, 1321, 1186, 1108, 1067, 1011, 839, 756 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ =2.90 (ddd, J = 8.4, 8.4, 16.4 Hz, 2 H), 3.20 (ddd, J = 6.0, 6.0, 16.4 Hz, 2 H), 3.69 (ddd, J = 6.0, 6.0, 13.0 Hz, 2 H), 4.22 (ddd, J = 6.0, 8.4, 13.0 Hz, 2 H), 6.08 (d, J = 7.6 Hz, 2 H), 6.13 (s, 2 H), 6.83–6.87 (m, 2 H), 7.16–7.21 (m, 4 H), 7.28 (d, J = 8.8 Hz, 4 H), 7.50 (d, J = 8.8 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.4, 43.2, 55.7, 123.8, 125.1, 127.7, 128.2, 128.4, 130.5, 131.8, 132.5, 134.2, 135.2, 170.5 ppm. $[\alpha]_D^{18}$ = –110.1 (c = 1.0, $CHCl_3$). LRMS (FAB): m/z = 629, 631, 633 $[M + H]^+$. HRMS (FAB): m/z calcd. for $C_{32}H_{27}Br_2N_2O_2$ 629.0439; found 629.0422. Crystal data: $C_{32}H_{26}N_2O_2Br_2$, mol. wt. = 630.38, monoclinic system, space group $P2_1$ (no. 4), a = 9.839 (2), b = 10.145 (2) c = 14.133 (3) Å, V = 1373.5 (4)3 Å, Z = 2, $D_{calcd.}$ = 1.524 g cm^{-3}, $F(000)$ = 636.00, μ(Mo-K_a) = 29.92 cm^{-1}.

Lattice constants and intensity data were measured using graphite-monochromated Mo-K_α radiation (λ = 0.71069 Å). Of the 8293 reflections that were collected, 3410 were unique (R_{int} = 0.037). Observations were made on a Rikagaku/MSC Mercury diffractometer. The structure was solved by direct methods using SIR97 and refined to a final R value of 0.041 and Rw = 0.059. CCDC-286847 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Oxidative Coupling of 9: (Table 3, Entry 5) A solution of CuCl (2.5 mg, 0.025 mmol) and diamine **6a** (6.5 mg, 0.025 mmol) in CH_3CN (0.25 mL) was stirred for 30 min and then CH_3CN (2.3 mL) was added. After addition of **9** (50 mg, 0.25 mmol) at 0 °C, the mixture was stirred for an additional 48 h. The reaction was quenched with 1 N HCl (5.0 mL) and extracted three times with AcOEt (10 mL). The combined organic layers were washed with brine and concentrated in vacuo to give the crude product. Purification by flash column chromatography on silica gel (hexane/AcOEt, 8:1) gave **10** as a yellow solid (30.0 mg, 0.15 mmol, 60%, 48% *ee*). The enantioselectivity was determined by chiral HPLC analysis on a Daicel Chiralpak AD column [hexane/*i*PrOH (9:1), 254 nm, flow rate: 1.0 mL min^{-1}; retention times: 9.4 min (*S* form: minor) and 15.5 min (*R* form: major)]. The absolute stereochemistry was determined based on the optical rotation value (see ref.[27]).

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[1] E. J. Roskamp, S. F. Pedersen, *J. Am. Chem. Soc.* **1987**, *109*, 3152–3154.

[2] E. J. Roskamp, S. F. Pedersen, *J. Am. Chem. Soc.* **1987**, *109*, 6551–6553.

[3] E. J. Roskamp, P. S. Dragovich, J. B. Hartung, S. F. Pedersen, *J. Org. Chem.* **1989**, *54*, 4736–4737.

[4] J. Syzmoniak, J. Besançon, C. Moïse, *Tetrahedron* **1992**, *48*, 3867–3876.

[5] J. Syzmoniak, J. Besançon, C. Moïse, *Tetrahedron* **1994**, *50*, 2841–2848.

[6] S. Arai, Y. Sudo, A. Nishida, *Chem. Pharm. Bull.* **2004**, *52*, 287–288.

[7] J. B. Hartung, S. F. Pedersen, *J. Am. Chem. Soc.* **1989**, *111*, 5468–5469.

[8] Y. Kataoka, K. Takai, K. Ohshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 365–368.

[9] Y. Kataoka, J. Miyai, M. Tezuka, K. Takai, K. Ohshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 369–372.

[10] Y. Kataoka, K. Takai, K. Ohshima, K. Utimoto, *J. Org. Chem.* **1992**, *57*, 1615–1618.

[11] J. B. Hartung, S. F. Pedersen, *Organometallics* **1990**, *9*, 1414–1417.

[12] M. Ortega, M. A. Rodriguez, P. J. Campos, *Tetrahedron* **2004**, *60*, 6475–6478.

[13] M. Shimizu, I. Suzuki, H. Makino, *Synlett* **2003**, 1635–1638.

[14] N. Kise, H. Oike, E. Okazaki, T. Yoshimoto, T. Shono, *J. Org. Chem.* **1995**, *60*, 3980–3982.

[15] D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627.

[16] K. Fuchibe, T. Akiyama, *Synlett* **2004**, 1282–1284.

[17] M. Shimizu, H. Makino, *Tetrahedron Lett.* **2001**, *42*, 8865–8868.

[18] G. J. Marcer, M. S. Sigman, *Org. Lett.* **2003**, *5*, 1591–1594.

[19] T. Shono, N. Kise, E. Shirakawa, H. Matsumoto, E. Okazaki, *J. Org. Chem.* **1991**, *56*, 3063–3067.

[20] For **5a**:I. S. Cho, C. P. Lee, P. S. Mariano, *Tetrahedron Lett.* **1989**, *30*, 799–802.

[21] For **5b**: F. S. Sancho, E. Mann, B. Herradon, *Synlett* **2000**, 509–513.

[22] A. T. Nielsen, *J. Org. Chem.* **1970**, *35*, 2498–2503.

[23] M. C. Elliott, E. Williams, S. T. Howard, *J. Chem. Soc., Perkin Trans. 2* **2002**, 201–203.

[24] M. C. Elliott, E. Williams, *Org. Biomol. Chem.* **2003**, *1*, 3038–3047.

[25] P. Cerutti, H. Schmid, *Helv. Chim. Acta* **1964**, *47*, 203–213.

[26] M. Nakajima, K. Kanayama, S. Hashimoto, *Tetrahedron Lett.* **1995**, *36*, 9519–9520.

[27] M. Nakajima, I. Miyoshi, K. Kanayama, S. Hashimoto, M. Noji, K. Koga, *J. Org. Chem.* **1999**, *64*, 2264–2271.

[28] X. Li, J. B. Hergley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500–5511.

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