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A Protecting-Group-Free Route to Chiral BINOL–Phosphoric Acids

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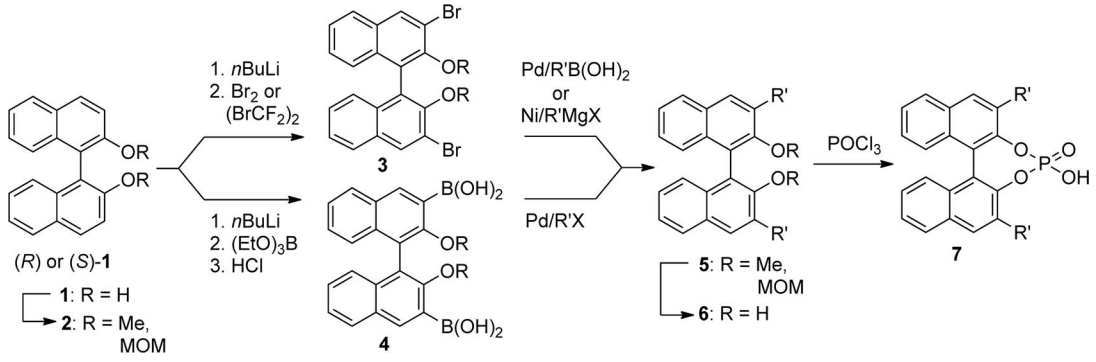
A two-step, protecting group-free route for the synthesis of 3,3′-disubstituted and 6,6′-disubstituted chiral BINOL–phosphoric acids has been realized starting from commercially available brominated BINOLs. This synthesis relies on the direct Suzuki coupling of brominated BINOL phosphoric acids. This synthetic strategy is more efficient compared to previous circuitous strategies involving protections and deprotections, and the process is higher yielding relative to the alternative two-step synthesis involving Suzuki coupling of the BINOL.

Introduction

BINOL–phosphoric acids (BNPHs) have emerged as an important and privileged family of compounds in asymmetric catalysis. Pioneering research by Akiyama[1] and Terada[2] have introduced 3,3′-disubstituted BNPHs as chiral Brønsted acid organocatalysts that mediate a spectacularly wide spectrum of carbon–carbon bond-forming reactions.[3] A wide variety of 3,3′-disubstituted BNPH derivatives has been designed and synthesized for the catalysis of a range of reactions.

In addition, BINOL–phosphates (BNPs) have been used successfully as chiral ligands of metal complexes to mediate enantioselective reactions. For example, Pirrung[4] and McKervey[5] employed $Rh_2(BNP)_4$ for reactions of diazocarbonyl compounds in C–H insertions, cyclopropanations, and aziridinations. Subsequently, extensive work by Hodgson investigated both 3,3′- and 6,6′-disubstituted BNP for the enantioselective rhodium-induced carbene cyclization cycloaddition cascade reaction.[6,7] The rare-earth complexes of BNP and 6,6′-disubstituted BNP were studied as catalysts for enantioselective Diels–Alder reactions.[8] The sodium salts of BNP derivatives have been investigated for the catalysis of the enantioselective Strecker reaction of ketimines.[9] More recently, asymmetric counteranion-directed catalysis (ACDC) has used chiral BNP in reactions mediated by gold, silver, and manganese complexes to effect enantioselectivity.[10]

While the reactions employing BNPH and BNP derivatives have seen an exponential growth, the strategies for their synthesis have remained consistent throughout the years. Scheme 1 shows the typical route for the synthesis of 3,3′-disubstituted BNPH **7** starting from BINOL (**1**). Protection of the hydroxy groups, often as ethers, is followed by *ortho*-lithiation to functionalize the 3- and 3′-positions. The lithiated BINOL derivative is then parlayed to either electrophile **3** through halogenation or nucleophile **4** through borylation. Substituents are then added by Suzuki–Miyaura coupling[11] or Kumada reactions.[11e,11k,12] The synthesis is completed through deprotection of the ethers and reaction with phosphorus oxychloride to generate the



Scheme 1. Typical synthesis of chiral 3,3′-BNPH **7**.

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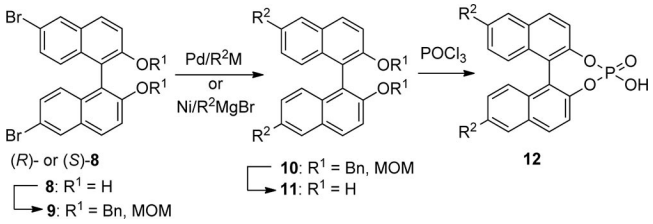
phosphoric acid functionality. A very similar sequence of reactions involving protections and deprotections is utilized for the synthesis of 6,6′-disubstituted BNPHs **12**, starting from commercially available 6,6′-dibromo-BINOL (**8**) as substrate (Scheme 2).[6,13]



Scheme 2. Typical synthesis of chiral 6,6′-BNPH **12**.

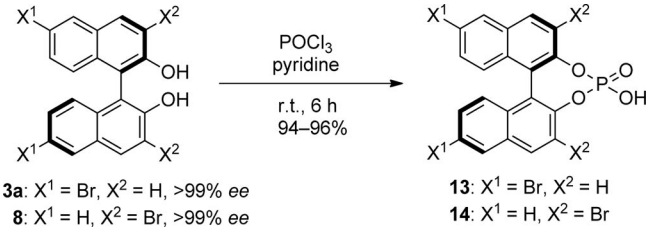
Herein we describe a straight-forward, protecting-group-free route for the synthesis of this important family of compounds, which employs direct Suzuki coupling in the presence of the phosphoric acid functionality.

Results and Discussion

In the course of our work on the application of the rhodium carbene cyclization–cycloaddition cascade reaction to synthesis,[14] the rhodium complex of **12a** as a chiral catalyst was required. The literature preparation of **12a** (Scheme 2) from **3a** involved multiple steps; moreover, Kumada coupling with dodecylmagnesium bromide provided **10** with variable yields.[6]

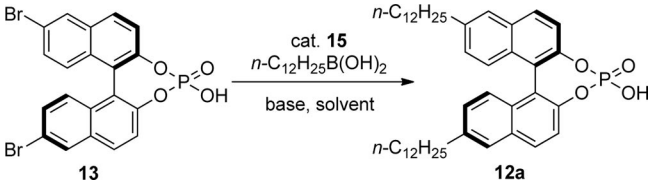
Our synthesis is based on the idea that the Suzuki coupling of brominated derivatives of BNPH would straightforwardly yield the corresponding substituted derivatives without necessitating the protection of any of the intermediates. This less circuitous route to **7** or **12** has not been reported in the literature and requires the Suzuki coupling to proceed successfully in the presence of the phosphoric acid or phosphate functionality. It is worthwhile to note that, while there have been some examples of Suzuki coupling reactions of alkyl phosphate, diphosphate, and triphosphate derivatives, proceeding generally in moderate yields,[15] the Suzuki coupling of aryl phosphates or phosphoric acid diesters have not been reported.[16]

We first explored the Suzuki coupling for the synthesis of 6,6′-disubstituted BNPH **12a**. BINOL **3a** is readily converted into corresponding BNPH **13** according to a literature procedure (Scheme 3).[11k] The optimizations of the Suzuki coupling of **13** are shown in Table 1. Initially, Suzuki coupling using the commercially available $PdCl_2(dppf)\cdot CH_2Cl_2$ complex (**15**) was tried, but it was not effective and resulted in decomposition of **13** (Table 1, Entry 1).[17] Upon changing to a weaker base (K_2CO_3), the reaction proceeded but was incomplete even after 60 h of refluxing in THF (Table 1, Entry 2). The application of Falck's conditions by the addition of Ag_2O failed to improve the reaction in this case (Table 1, Entry 3).[18] We then examined the reaction at higher temperatures in other solvents. While the use of DMF resulted in the decomposition of **13**, the Suzuki coupling was complete at a comparable temperature in refluxing DME to give an 81% yield of **12a** (Table 1, Entry 5). The use of water in the reaction was deleterious to the rate of conversion (Table 1, Entries 6 and 7).



Scheme 3. Synthesis of BNPHs **13** and **14**.

Table 1. Optimization of Suzuki coupling of **13**.

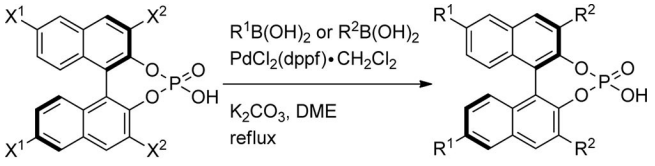


Entry	Base (equiv.)	Solvent	*T* [°C]	*t* [h]	Yield [%]
1	NaOH (5)	1,4-dioxane	101 (reflux)	24	dec.
2	K_2CO_3 (9)	THF	66 (reflux)	60	43
3	K_2CO_3 (9)	THF[a]	66 (reflux)	60	39
4	K_2CO_3 (9)	DMF	90	24	dec.
5	K_2CO_3 (9)	DME	85 (reflux)	60	81
6	K_2CO_3 (5)	THF/H_2O (10:1)	reflux	16	N.R.
7	K_2CO_3 (9)	DME/H_2O (10:1)[b]	reflux	24	N.R.

[a] Ag_2O (3 equiv.). [b] $Pd(PPh_3)_4$ used as catalyst.

Thus, **12a** was synthesized efficiently in two high-yielding steps from **3a**. Using the optimized conditions, we examined the Suzuki coupling of both **13** and **14** (Scheme 3) with various boronic acids (Table 2). Phenylboronic acid reacted

Table 2. Suzuki coupling of brominated BNPHs **13** and **14**.



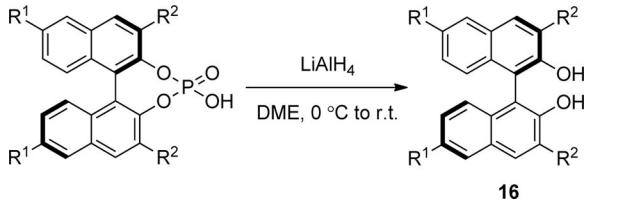
Entry	X^1	X^2	R^1	R^2	*t* [h]	Yield [%]	$[\alpha]_D^{20}$
1	Br	H	*n*-$C_{12}H_{25}$	H	60	**12a**, 81	–285.1
2	Br	H	Ph	H	48	**12b**, 92	–278.8
3	H	Br	H	Ph	48	**7a**, 93	–328.5
4	H	Br	H	4-(*t*Bu)C_6H_4-	48	**7b**, 95	–343.1
5[a]	H	Br	H	4-(*t*Bu)C_6H_4-	48	**7b**, 68[b]	n.d.
6	H	Br	H	mesityl	96	**7c**, 61	–155.9

[a] $Pd(PPh_3)_4$ used as catalyst. [b] Monoarylated BNPH (27% yield) also obtained.

more readily under similar conditions to generate a very good yield of **12b** (Table 2, Entry 2). At the sterically more congested 3,3′-positions, aryl boronic acids still underwent Suzuki coupling readily in excellent yields (Table 2, Entries 3 and 4). However, for a hindered boronic acid such as mesityl, the coupling reaction was less efficient (Table 2, Entry 6). The use of $Pd(PPh_3)_4$ as catalyst was less effective (Table 2, Entry 5).

The BNPHs were reduced by using $LiAlH_4$ to afford the corresponding BINOLs in high yield (Table 3).[19] No racemization occurred during the synthesis or the reduction, as shown by the enantiomeric excess values of the BINOLs thus obtained, determined by chiral HPLC (Table 3).

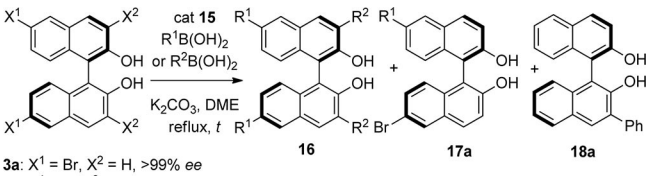
Table 3. Reduction of BNPHs to BINOLs.



Entry	Substrate	R^1	R^2	t [h]	Yield [%]	$[a]_D^{20}$	*ee* [%]
1	**12a**	n-$C_{12}H_{25}$	H	4	**16a**, 93	–44.0	>99
2	**12b**	Ph	H	4	**16b**, 92	–243.4	>99
3	**7**	H	Ph	8	**16c**, 91	+68.7	>99

We then investigated whether the two operations could be reversed, that is, to subject BINOLs **3a** and **8** to Suzuki coupling followed by phosphate ester formation. We were cautioned to the known racemization of chiral BINOLs, occurring especially with heating under acidic or basic conditions.[20] Having a similar aim of devising a synthesis of chiral BNP without the use of protecting groups, Bartoszek et al. recently reported the direct Suzuki coupling of 3,3′-dibromo–H8–BINOL, which was followed by esterification with phosphoryl chloride to yield the substituted BNPH.[21] This Suzuki coupling of the BINOLs was successfully carried out at ambient temperature using $Pd(OAc)_2$ and Beller's ligand, PAd_2Bu.[22] Under our present conditions, although the Suzuki coupling of BINOL **3a** with an alkylboronic acid proceeded, the reaction was more sluggish, and much monosubstituted product **17a** was obtained (Table 4, Entry 1). Attempts to drive the reaction to completion with prolonged heating resulted in a significantly lower yield of the desired product (Table 4, Entry 2). With more reactive phenylboronic acid, Suzuki coupling of **8** occurred more readily but nevertheless with a diminished yield compared to the reaction of **14** (Table 4, Entry 3). Notably, debromination is a side reaction under these conditions, and a slight decrease in the enantiomeric excess of **16c** was observed. In contrast, even with prolonged heating, racemization by rotation about the C1–C1′ is obviated in the Suzuki coupling of **14** bearing the phosphoric acid tether.[20]

Table 4. Suzuki coupling of brominated BINOLs **3a** and **8**.



3a: X^1 = Br, X^2 = H, >99% *ee*
8: X^1 = H, X^2 = Br, >99% *ee*

Entry	BINOL	t [h]	R^1	R^2	Yield of **16** [%]	Yield of **17** [%]	*ee* [%]
1	**3a**	42	$C_{12}H_{25}$	H	**16a**, 23	**17a**, 39	98
2	**3a**	84	$C_{12}H_{25}$	H	**16a**, 45	trace	98
3	**8**	48	H	Ph	**16c**, 79[a]	trace	94

[a] **18a** (9% yield) also obtained.

Conclusions

We have shown that chiral BINOL phosphoric acids could be accessed by a protecting-group-free route from brominated BINOLs **3a** and **8**, both of which are commercially available, in two steps through the direct Suzuki coupling of the corresponding BNPH. No loss of *ee* was observed. This synthesis is much more efficient compared to previous strategies involving protections and deprotections, cutting the number of steps required by half, and the procedure is higher yielding relative to the alternative two-step synthesis involving the direct Suzuki coupling of the BINOL. The protecting-group-free strategy reported herein should be useful for the synthesis of chiral, substituted BNPHs owing to the growing importance, applications, and versatility of this family of compounds, where a large number of derivatives are invariably needed in each screening exercise.

Experimental Section

General Methods: All anhydrous reactions were performed in oven-dried round-bottomed flasks under a positive pressure of dry argon. Air- and moisture-sensitive compounds were introduced by syringes or cannulae using standard inert atmosphere techniques. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel plates, Kieselgel 60 F254 with a 0.2-mm thickness. Components were visualized by illumination with short-wavelength ultraviolet light and/or staining. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh ASTM) or Sigma–Aldrich alumina (activated Al_2O_3, neutral, Brockmann I). Solvents and chemicals were purified according to standard procedures. All solvents used for reactions were distilled or dried by passing through drying columns. Tetrahydrofuran, 1,4-dioxane, DME, pyridine, and DMF (under reduced pressure) were additionally distilled from CaH_2. BNPHs **13** and **14** were prepared according to literature procedures.[11k] ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform ($CDCl_3$) or a mixture of deuteriochloroform with [D_4]MeOH (CD_3OD), with tetramethylsilane (TMS) as an internal standard at ambient temperature with a Bruker Avance 400 spectrometer, operating at 400 MHz for ^1H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. All spectra were calibrated at δ = 0.00 ppm for ^1H spectra (TMS) and at 77.16 ppm for ^{13}C spectra ($CDCl_3$). Splitting pat-

terns are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. IR absorption spectra were recorded as solutions in CH_2Cl_2 with a Bio-Rad FTS 165 spectrometer from 4000 to 400 cm^{-1}. Electron impact (EI) mass spectrometry was recorded with a Finnigan MAT 95 mass spectrometer at low and high resolutions, with accurate mass reported for the molecular ion $[M]^+$ or the next largest fragment thereof. Optical rotations were recorded with a Perkin–Elmer 343 Polarimeter. Analytical HPLC was carried out with a Waters 1525 Binary HPLC Pump system, equipped with a Waters 2707 autosampler operating using Breeze2 software and a Waters 2489 variable wavelength UV/Vis detector.

General Experimental Procedure for Suzuki Coupling Reactions: A mixture of **13** or **14** (0.1 mmol), aryl- or alkylboronic acid (0.395 mmol), **15** (0.010 mmol), and K_2CO_3 (0.85 mmol) in dry DME (6 mL) was heated at reflux under an atmosphere of argon for 48 to 60 h, while the reaction progress was monitored by TLC. After the reaction was complete, it was cooled to room temperature. The reaction mixture was adjusted to pH 3 by the addition of 2 M HCl, and it was then filtered and concentrated in vacuo. The residue was dissolved in acetone (or hexane, in the case of **12a**) and filtered through a pad of Celite. After removing the volatiles in vacuo, the residue was purified firstly by flash column chromatography using a short alumina column (20% MeOH in CH_2Cl_2/20% AcOH in MeOH), and secondly by flash chromatography on silica gel (5–35% MeOH in CH_2Cl_2) to give **7** or **12** as product.

(*R*)-12a:[7b] Yield: 81%; viscous colorless oil. $[\alpha]_D^{20}$ = –285.1 (*c* = 0.70, $CHCl_3$) {ref.[7b] $[\alpha]_D^{20}$ = –266.2 (*c* = 0.7, $CHCl_3$)}. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:1): δ = 7.88 (d, *J* = 8.6 Hz, 2 H), 7.67 (s, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 2.75 (t, *J* = 7.6 Hz, 4 H), 1.74–1.66 (m, 4 H), 1.40–1.27 (m, 36 H), 0.88 (t, *J* = 6.7 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:1): δ = 147.8, 139.1, 131.1, 130.5, 129.3, 127.3, 126.5, 126.2, 121.7, 121.0, 35.3, 31.5, 30.8, 29.2, 29.2, 29.2, 29.1, 28.9, 22.2, 13.4 ppm. ^{31}P NMR (162 MHz, $CD_3OD/CDCl_3$ = 1:1): δ = 4.2 ppm.

(*R*)-12b:[10] Yield: 92%; white solid. $[\alpha]_D^{20}$ = –278.8 (*c* = 0.50, CH_2Cl_2). ^1H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:2): δ = 8.10 (br. s, 2 H), 7.95 (d, *J* = 8.5 Hz, 2 H), 7.71–7.67 (m, 4 H), 7.63 (d, *J* = 8.7 Hz, 2 H), 7.57 (dd, *J* = 8.7, 1.3 Hz, 2 H), 7.50 (d, *J* = 8.9 Hz, 2 H), 7.47–7.42 (m, 4 H), 7.38–7.33 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:2): δ = 148.8, 148.7, 140.2, 137.4, 131.4, 130.4, 128.7, 127.4, 127.2, 126.9, 125.7, 125.6, 122.0, 121.8 ppm. ^{31}P NMR (162 MHz, $CD_3OD/CDCl_3$ = 1:2): δ = 2.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3055, 2360, 1265, 1149, 768, 710 cm^{-1}. MS (FAB+): *m*/*z* = 523.4 $[M + Na]^+$, 501.1 $[M + H]^+$.

(*R*)-7a:[11j] Because the monophenylated product was inseparable from **7a**, to ensure complete reaction, extra $PhB(OH)_2$ (2 equiv.), **15** (0.05 equiv.), and K_2CO_3 (4 equiv.) were used. Yield: 93%; white solid. $[\alpha]_D^{20}$ = –328.5 (*c* = 1.02, $CHCl_3$) {ref.[11j] $[\alpha]_D^{27}$ = –283.5 (*c* = 0.99, $CHCl_3$)}. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 7.98 (br. s, 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.75–7.72 (m, 4 H), 7.47–7.42 (m, 2 H), 7.35–7.31 (m, 4 H), 7.30–7.22 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 146.6, 146.5, 138.5, 134.8, 132.7, 131.6, 131.4, 130.5, 128.7, 128.4, 127.6, 127.3, 126.7, 125.9, 123.6 ppm. ^{31}P NMR (162 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 2.3 ppm.

(*R*)-7b:[23] Yield: 95%; white solid. $[\alpha]_D^{20}$ = –343.1 (*c* = 1.06, $CHCl_3$). ^1H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 7.97 (br. s, 2 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.68–7.65 (m, 4 H), 7.46–7.42 (m, 2 H), 7.36–7.33 (m, 4 H), 7.29–7.24 (m, 4 H), 1.27 (s, 18 H) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 149.8, 145.9, 145.8, 134.9, 133.9, 132.0, 130.9, 130.6, 129.4, 128.0, 126.7, 125.9, 125.2, 124.6, 122.9, 34.2, 31.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3024, 2962, 2360, 1519, 1427, 1226, 1203, 1111, 972, 841, 795 cm^{-1}. MS (FAB+): *m*/*z* = 652.2, 651.2 $[M + K]^+$, 635.2 $[M + Na]^+$, 612.2 $[M]^+$.

(*R*)-7c:[11j] Yield: 61%; white solid. $[\alpha]_D^{20}$ = –155.9 (*c* = 0.80, $CHCl_3$) {ref.[11j] $[\alpha]_D^{26}$ = –93.2 (*c* = 1.08, $CHCl_3$)}. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 7.91 (d, *J* = 8.2 Hz, 2 H), 7.71 (br. s, 2 H), 7.48–7.44 (m, 2 H), 7.31–7.26 (m, 4 H), 6.89 (s, 2 H), 6.81 (s, 2 H), 2.28 (s, 6 H), 2.15 (s, 6 H), 2.00 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 146.7, 137.0, 136.9, 136.2, 134.4, 132.8, 132.1, 130.8, 130.7, 127.8, 127.0, 126.5, 125.8, 124.8, 122.3, 20.6, 20.5, 19.6 ppm. ^{31}P NMR (162 MHz, $CD_3OD/CDCl_3$ = 1:3): δ = 4.1 ppm.

General Experimental Procedure for the Reduction of Chiral BNPH: A solution of chiral BNPH (0.06 mmol) in DME (0.8 mL) was transferred carefully to a suspension of $LiAlH_4$ (0.36 mmol) in DME (0.8 mL) at 0 °C. The reaction was stirred and warmed to room temperature. The reaction progress was monitored by TLC. When the reaction was complete, the excess amount of $LiAlH_4$ was quenched by the dropwise addition of H_2O at 0 °C, and the acidity of the solution was adjusted to pH 5–6 by the addition of 2 M HCl. The resultant cloudy mixture was suspended in acetone (10 mL) and filtered through filter paper. After concentrating under reduced pressure, the crude product was dissolved in EtOAc (12 mL) and washed by brine (5 mL). The organic components were dried with anhydrous $MgSO_4$, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography using silica gel (5–20% EtOAc in hexane) to give **16**.

(*R*)-16a:[7b] Yield: 93%; viscous colorless oil. $[\alpha]_D$ = –44.0 (*c* = 0.80, $CHCl_3$) {ref.[7b] $[\alpha]_D^{20}$ = –51.4 (*c* = 1.0, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.9 Hz, 2 H), 7.66 (br. s, 2 H), 7.34 (d, *J* = 8.9 Hz, 2 H), 7.16 (dd, *J* = 8.6, 1.6 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 4.98 (br. s, 2 H), 2.71 (t, *J* = 7.7 Hz, 4 H), 1.68–1.61 (m, 4 H), 1.39–1.23 (m, 36 H), 0.87 (t, *J* = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 138.8, 131.8, 131.0, 129.8, 129.2, 127.0, 124.3, 117.8, 111.0, 36.0, 32.1, 31.6, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 22.8, 14.3 ppm. HPLC (Chiralcel OD, hexane/2-propanol = 48:2, 0.5 mL min^{-1}): >99% *ee*.

(*R*)-16b:[24] Yield: 92%; white solid. $[\alpha]_D^{20}$ = –243.4 (*c* = 0.65, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 1.8 Hz, 2 H), 8.05 (d, *J* = 8.9 Hz, 2 H), 7.69–7.65 (m, 4 H), 7.60 (dd, *J* = 8.7, 1.9 Hz, 2 H), 7.49–7.42 (m, 6 H), 7.38–7.34 (m, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 141.0, 137.1, 132.7, 131.9, 129.9, 129.0, 127.4, 127.4, 127.4, 126.5, 124.9, 118.4, 110.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3525, 3055, 2361, 1597, 1497, 1257, 1149, 702 cm^{-1}. HRMS (EI+): calcd. for $C_{32}H_{22}O_2$ $[M]^+$ 438.1620; found 438.1610. HPLC (Chiralpak IC-3, hexane/2-propanol = 90:10, 1.0 mL min^{-1}): >99% *ee*.

(*R*)-16c:[12d] Yield: 91%; white solid. $[\alpha]_D^{20}$ = +69.7 (*c* = 0.98, $CHCl_3$) {ref.[12d] $[\alpha]_D$ = +69.1 (*c* = 1.00, $CHCl_3$)}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br. s, 2 H), 7.91 (d, *J* = 7.9 Hz, 2 H), 7.74–7.71 (m, 4 H), 7.50–7.46 (m, 4 H), 7.42–7.36 (m, 4 H), 7.33–7.29 (m, 2 H), 7.24–7.22 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 137.6, 133.1, 131.5, 130.8, 129.7, 129.6, 128.6, 128.6, 127.9, 127.5, 124.5, 124.4, 112.5 ppm. HPLC (Chiralpak IC-3, hexane/2-propanol = 90:10, 1.0 mL min^{-1}): >99% *ee*.

(*R*)-17a: Viscous colorless oil. $[\alpha]_D^{20}$ = –79.5 (*c* = 0.61, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 2.0 Hz, 1 H), 7.91 (d, *J* = 8.9 Hz, 1 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.66 (br. s, 1 H), 7.40 (d, *J* = 9.0 Hz, 1 H), 7.37–7.32 (m, 2 H), 7.17 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.04–6.99 (m, 2 H), 5.11 (s, 1 H), 4.92 (s, 1 H), 2.71 (t, *J* =

7.8 Hz, 2 H), 1.68–1.63 (m, 2 H), 1.32–1.24 (m, 18 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 153.1, 152.2, 139.0, 132.2, 131.7, 131.3, 130.8, 130.7, 130.5, 129.8, 129.4, 127.1, 126.3, 124.0, 119.1, 118.0, 117.8, 111.7, 110.2, 35.9, 32.1, 31.6, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 22.8, 14.3 ppm. IR (KBr): $\tilde{\nu}$ = 3526, 2932, 2854, 1597, 1504, 1358, 1265, 1180, 895, 748 cm^{-1}. HRMS: calcd. for $C_{32}H_{37}O_2Br$ $[M]^+$ 532.1977; found 532.1971.

(*R*)-18a:[25] White solid. $[\alpha]_D^{20}$ = +115.4 (c = 0.14, CH_2Cl_2) {ref.[25] $[\alpha]_D^{30.5}$ = +132.0 (c = 1.18, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H), 7.99 (d, J = 8.9 Hz, 1 H), 7.94–7.89 (m, 2 H), 7.74–7.72 (m, 2 H), 7.52–7.47 (m, 2 H), 7.43–7.35 (m, 4 H), 7.34–7.29 (m, 2 H), 7.23 (d, J = 8.3 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 150.4, 137.5, 133.6, 133.1, 131.6, 131.5, 130.8, 129.7, 129.6, 128.6, 128.6, 128.6, 128.0, 127.6, 124.5, 124.4, 124.3, 124.1, 117.9, 111.9, 111.6 ppm. HRMS (EI+): calcd. for $C_{26}H_{18}O_2$ $[M]^+$ 362.1307; found 362.1297.

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