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Scalable Synthesis of Enantiopure Bis-3,4-diazaphospholane Ligands for Asymmetric Catalysis

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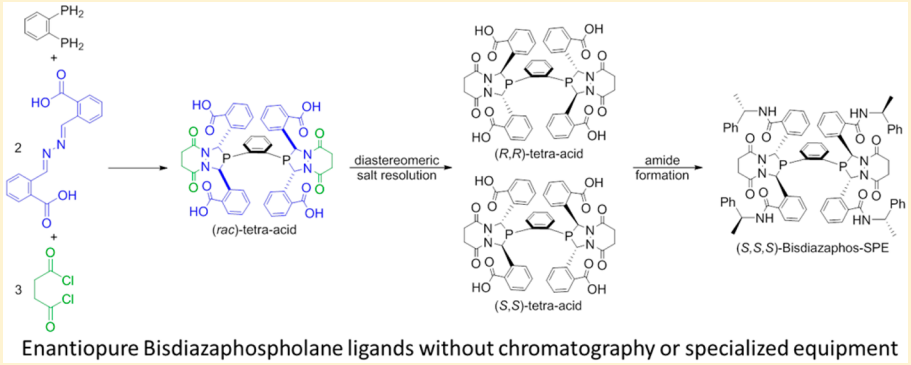
Supporting Information



Enantiopure Bisdiazaphospholane ligands without chromatography or specialized equipment

ABSTRACT: An optimized route to enantiopure tetra-carboxylic acid and tetra-carboxamide bis(diazaphospholane) ligands that obviates chromatographic purification is presented. This synthesis, which is demonstrated on 15 and 100 g scales, features a scalable classical resolution of tetra-carboxylic acid enantiomers with recycling of the resolving agent. When paired with a rhodium metal center, these bis(diazaphospholane) ligands are highly active and selective in asymmetric hydroformylation applications.

The family of bis(diazaphospholane) (BDP) ligands exhibits high reactivity, regioselectivity, and enantioselectivity for asymmetric hydroformylation (AHF) when paired with a rhodium metal center.[1] BDP-ligated hydroformylation catalysts are highly active under mild conditions (e.g., 150 psi of synthesis gas). Such modest pressures enable reactions to be performed in glass pressure bottle reactors,[2] rather than more expensive metal autoclave reactors. The development of the BDP class of ligands has expanded the availability of α-chiral aldehydes via atom economical, catalytic transformations. BDP ligands are extensible and allow many variants to be produced from a single precursor. For example, libraries of tetra-carboxamide BDPs have been reported as both free[3] and immobilized[4] ligands.

The limited commercial availability and inconvenient synthesis of BDP ligands restricts their use.[1g] Herein we demonstrate efficient and scalable synthesis of enantiopure BDP ligands, without the use of chromatography or specialized equipment. The procedure (Scheme 1) comprises synthesis of a racemic tetracarboxylic acid intermediate **2**, resolution of this intermediate by selective crystallization of diastereomeric salts of the tetra-acid, and coupling of the enantiopure BDP tetracarboxylic acid **2** and enantiopure α-methylbenzylamine to the BDP tetracarboxamide **6**. Pure material is obtained by recrystallization and without chromatography throughout the entire process. This procedure is scalable from grams to hundreds of grams, uses equipment and techniques common to synthetic organic laboratories, and provides access to a family of enantiopure bisphosphine ligands that are useful in catalysis. These features should facilitate commercial production or smaller scale, local synthesis of these unique ligands.

Synthesis of BDP ligands begins with the formation of the azine **1** that ultimately reacts with a primary phosphine to form phospholane ring structures. Following a modified procedure (Scheme 2) from the literature,[5] azine **1** was synthesized in high yields (95%) and carried on to the next step without further purification.

With azine **1** in hand, we directed our efforts to the optimized synthesis of the racemic tetra-carboxylic acid ligand **2** (Scheme 3) which is a critical intermediate in making BDP ligands. Starting from the previously published procedure,[1a] we noticed that the yield exhibited a strong dependence on reaction temperature, and that rapid addition of succinyl chloride to a mixture of *o*-bis(phosphino)benzene and **1** resulted in a 5−10 °C exothermic warming of the mixture. Therefore, we effected slow initial addition of the acid chloride to allow better temperature equilibration with the cold bath.

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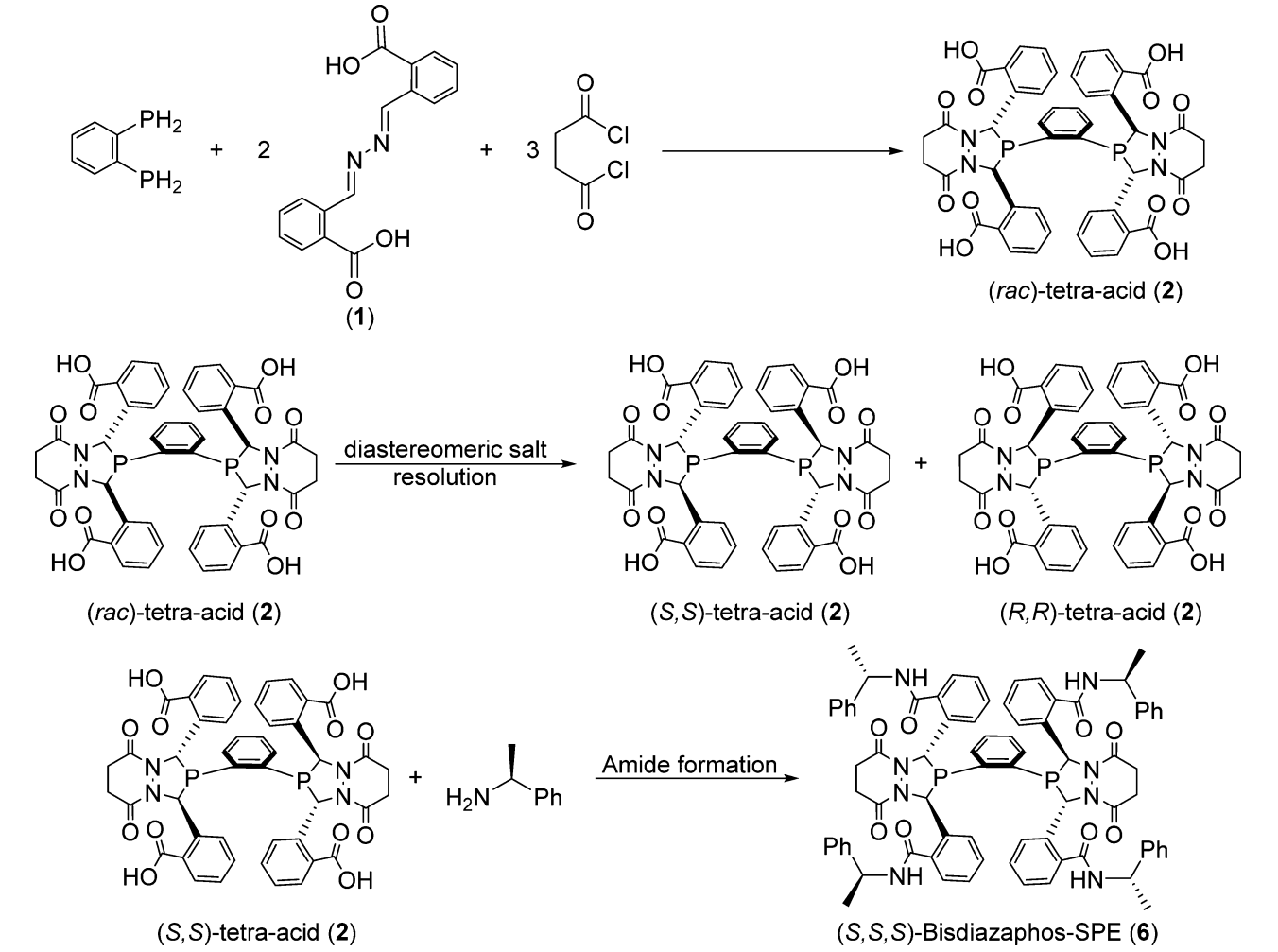
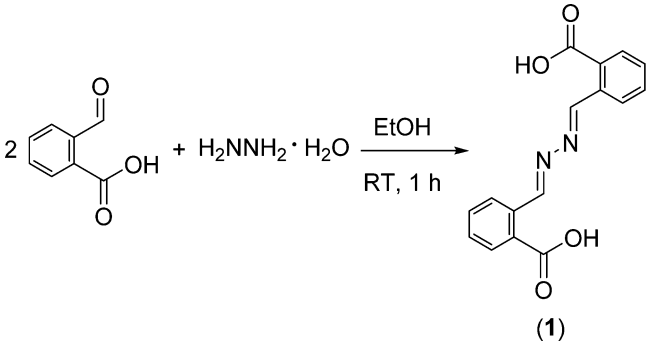
Scheme 1. Route to (*S,S,S*)-Bisdiazaphos-SPE



Scheme 2. Synthesis of Azine 1



This procedure led to higher isolated yields (~40%) of the C_2 symmetric (*rac*)-tetra-acid **2**, which selectively precipitates from solution. The remainder of the material appears to be lower symmetry stereoisomers that remain in solution.[6]

The racemic tetra-acid **2** is resolved (Scheme 4) by the formation of diastereomeric salts. Separable salts are formed by addition of enantiopure (1*R*,2*R*)-pseudoephedrine to **2**, introduction of an acetonitrile/water mixture, and warming to dissolve the solids. Upon cooling this mixture, the enantiopure salt **3**, [(1*R*,2*R*)-pseudoephedrine]$_4$·[(*S,S*)-tetra-acid **2**], precipitates from solution. The diastereopurity of the resulting salt is conveniently revealed by ^{31}P NMR which exhibits resonances near 1 and 3 ppm for the two diastereomeric salts. The [(1*R*,2*R*)-pseudoephedrine)]$_4$·[(*S,S*)-**2**] salt **3** was found to be diastereomerically pure after one recrystallization, and the absolute stereochemistry was established by X-ray crystallography and by derivatization to form known materials.[7]

Treatment of a methanol solution of the [(1*R*,2*R*)-pseudoephedrine)]$_4$(*S,S*-**2**) salt **3** with 3 M aqueous HCl generates the free acid (*S,S*)-**2**, which precipitates from the solution as enantiomerically pure material (Scheme 5). The overall yield of resolved (*S,S*)-**2** starting from the diastereomeric salt is 88% and has a potency[8] of 93%. The other enantiomer of the tetra-acid, (*R,R*)-**2** can be recovered in enantioenriched form from the mother liquor of the first resolution step in similar fashion (Scheme 6). This material may be resolved to enantiopure state by precipitation with the (1*S*,2*S*) enantiomer of pseudoephedrine.

Following the recovery of resolved tetra-acid **2**, treatment of the coproduct pseudoephedrine·HCl salt with NaOH, followed by extraction with CH_2Cl_2 (Scheme 7), yields pseudoephedrine in 88% yield for use in later resolutions. Thus, the chiral resolving agent is recycled.

The tetra-carboxamide ligand (*S,S,S*)-Bisdiazaphos-SPE **5** is synthesized (Scheme 8) by coupling of (*S,S*)-tetra-acid **2** with (*S*)-α-methylbenzylamine in the presence of propylphosphonic anhydride (T3P). After coupling, the BDP ligand was isolated as a crude solid (technical **5**) and recrystallized from acetone

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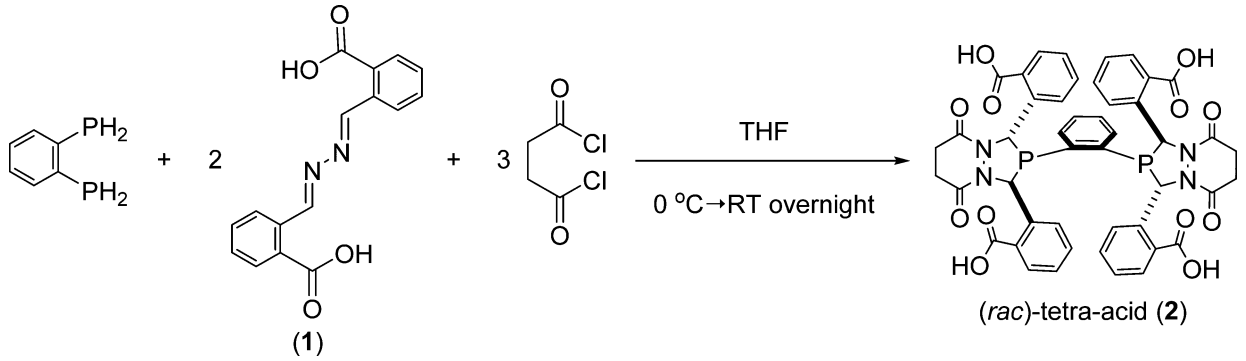
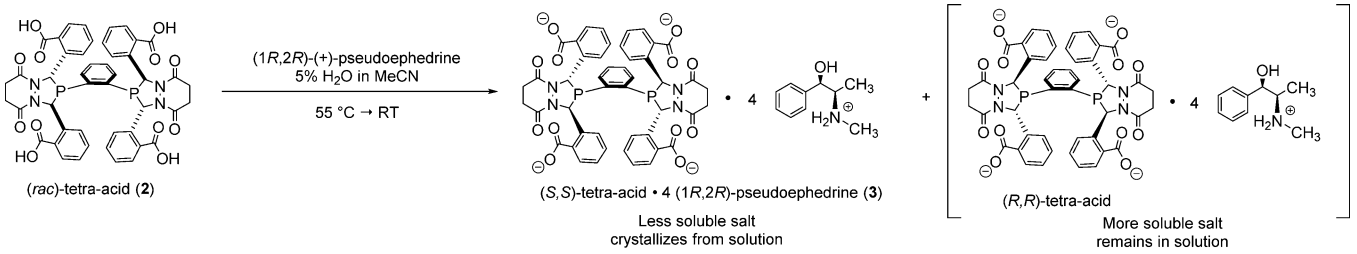
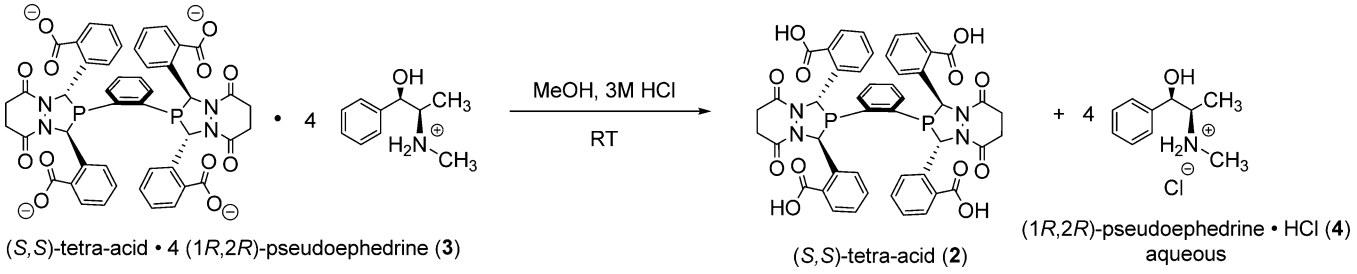
Scheme 3. Synthesis of Racemic Tetra-carboxylic Acid Intermediate 2



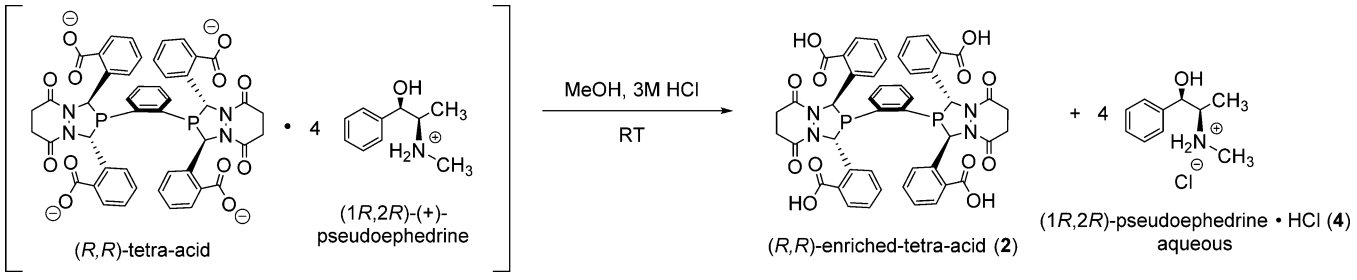
Scheme 4. Resolution of (*rac*)-Tetra-acid 2 by Diastereomeric Salt Formation



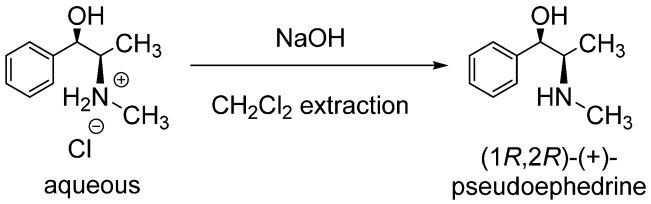
Scheme 5. Isolation of Enantiopure Tetra-acid 2 from Pseudoephedrine



Scheme 6. Recovery of Enantioenriched Tetra-acid 2 from the Mother Liquor of Scheme 4



Scheme 7. Recovery of Pseudoephedrine from Its Aqueous HCl Salt



(Scheme 9) to yield purified (90% potent)[9] solid **6** as an acetone solvate in 71% overall yield from **2**.

■ SUMMARY

In summary, a convenient route to enantiopure BDP ligands, in either absolute configuration, features classical resolution of the C_2-symmetric tetra-acid enantiomers of **2** via formation of diastereomeric salts with enantiopure pseudoephedrine. Resolution of racemic tetra-acid **2** leads to 88% recovery of enantiopure (*S*,*S*)-tetra-acid **2**. The resolving agent, (*R*,*R*)-pseudoephedrine, is recovered in 88% yield and can be used for further resolutions. Amide formation using enantiopure **2** produces (*S*,*S*,*S*)-Bisdiazaphos-SPE **6** in 71% yield over the coupling and recrystallization steps. The significance of this route is that it enables access to this class of chiral ligands through efficient and scalable nonchromatographic resolution

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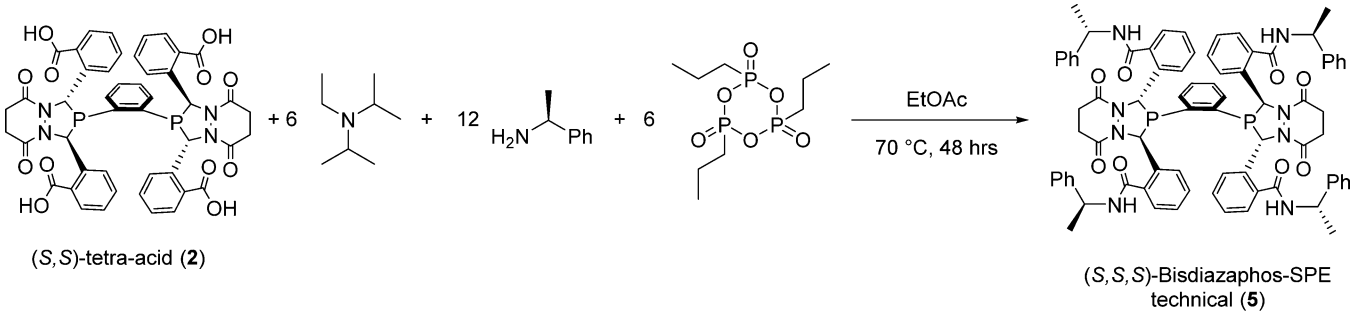
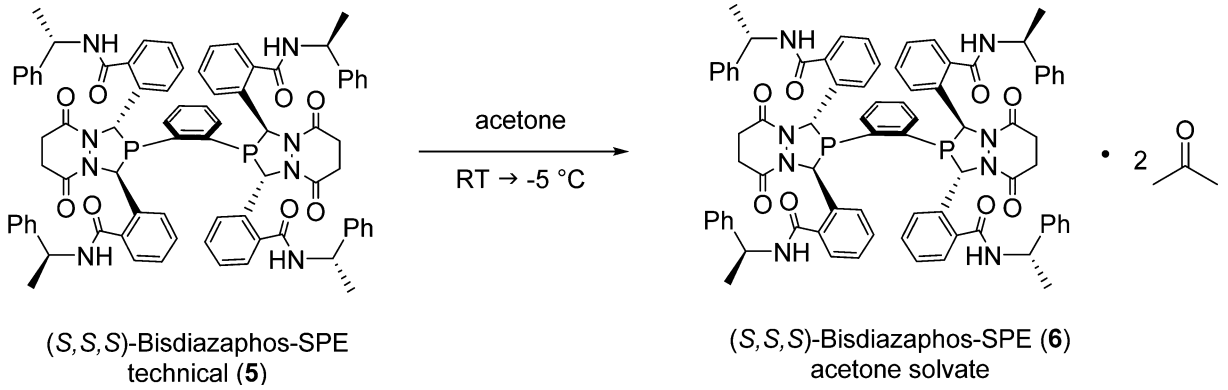
Scheme 8. Synthesis of (*S,S,S*)-Bisdiazaphos-SPE 5 via Amide Coupling of Enantiopure (*S,S*)-Tetra-acid 2



Scheme 9. Recrystallization of Crude BDP Ligand 5 To Yield Purified BDP Ligand 6



of the racemic intermediate. Improved availability of these novel ligands facilitates greater implementation of highly active and selective asymmetric hydroformylation transformations.

EXPERIMENTAL SECTION

General Methods. Solvents were dried by safety columns or degassed by stirring under an inert gas for prolonged periods, unless otherwise noted. Succinyl chloride was vacuum distilled and degassed prior to use and stored as a colorless liquid in a bomb flask covered in aluminum foil. Ethyl acetate was dried over K_2CO_3, filtered, sparged with N_2, and stored in a bomb flask. T3P solution (50 wt % in ethyl acetate) was transferred to a bomb flask and used as received. (*R*)- and (*S*)-α-methylbenzylamine were degassed by four freeze−pump−thaw cycles and stored in a glovebox. Acetone for recrystallization was used as received.

2,2′-(Azinodimethylidyne)bis-benzoic Acid (1). Bench Scale. 2-Carboxybenzaldehyde (31.6 g, 210 mmol) was dissolved in 300 mL of 95% ethanol in a 1 L beaker open to air. Hydrazine monohydrate (5.1 mL, 5.2 g, 105 mmol) was added dropwise to the stirred solution, and the resulting yellow suspension was stirred 1 h at room temperature. The reaction mixture was vacuum filtered through qualitative filter paper using a Buchner funnel connected to an aspirator. The filter cake was dried under vacuum (0.06 mmHg) for 2 h to yield the azine (**1**) as a yellow solid (29.70 g, 95% yield).

Large Scale. To a 12 L flask open to air was added 2-carboxybenzaldehyde (249.5 g, 1.629 mol) and 3.6 L of ethanol. The mixture was stirred until dissolved, and then hydrazine (35% in H_2O, 75 mL, 76 g, 0.83 mol) was added via addition funnel over 10 min. The solution immediately turned yellow and formed a slurry within 2 min of beginning the addition. The solution temperature increased from 17.4 to 28.4 °C. The slurry was allowed to cool and stir for 4 h before being cooled in an ice bath to <5 °C. The slurry was filtered over polypropylene and washed with 800 mL of ethanol. The solid was dried in a vacuum oven (90 mmHg) overnight at 40 °C to yield a powdery yellow solid (231 g, 95.7% yield).

The NMR spectrum for this compound shows a major and minor conformer which are in exchange with each other. See Supporting Information (SI) for more information.

^{1}H NMR (500 MHz, DMSO-d_6) δ 13.40 (s, 2H major, 1H minor), 9.31 (s, 2H major), 8.95 (d, *J* = 8.0 Hz, minor), 8.60 (s, minor), 8.14 (d, *J* = 7.6 Hz, 2H major), 7.96 (d, *J* = 7.2 Hz, 2H major), 7.93 (d, *J* = 3.8 Hz, minor), 7.87 (d, *J* = 7.0 Hz, minor), 7.83 (dt, *J* = 6.9, 4.2 Hz, minor), 7.78 (d, *J* = 7.8 Hz, minor), 7.69 (t, *J* = 7.3 Hz, 2H major), 7.63 (t, *J* = 7.5 Hz, 2H major), 7.52 (t, *J* = 7.5 Hz, minor), 7.40 (t, *J* = 7.5 Hz, minor), 6.92 (d, *J* = 8.0 Hz, minor).

^{13}C NMR (126 MHz, DMSO-d_6) δ 169.0, 168.2, 167.9, 160.9, 159.6, 144.9, 135.2, 134.3, 133.8, 133.6, 132.1, 131.8, 130.9, 130.5, 130.2, 129.9, 129.4, 128.2, 127.6, 126.7, 125.7, 124.5, 124.1, 39.5.

rel-2,2′,2″,2‴-(1,2-Phenylenebis((1R,3R)-tetrahydro-5,8-dioxo-1H-(1,2,4)diazaphospholo(1,2-a)pyridazine-2,1,3(3H)-triyl))tetrakis-benzoic Acid (2). Bench Scale. 2,2′-(Azinodimethylidyne)bis-benzoic acid (**1**) (20.88 g, 70.47 mmol) was added to an oven-dried single-necked 1 L round-bottom Schlenk flask equipped with a Teflon-coated stir bar, glass stopcock, and a rubber septum. The flask was then subjected to three cycles of evacuation followed by refilling with nitrogen to remove air. Dry, inert THF (500 mL, 100 mL/g phosphine) was added via cannula transfer from an inert bomb flask, and then the 1,2-bis(phosphino)benzene (5.0 g, 35.2 mmol) was added via syringe. ***Caution:*** *1,2-Bis(phosphino)benzene is pyrophoric, and appropriate air-free handling techniques must be used!* The full contents of the 5 g ampule were used, and the ampule was rinsed with THF (2 × 1 mL). Carrying the syringe in a sealed secondary container is recommended. Excess phosphine can be stored in the glovebox. The flask was submerged in a 0 °C ice−water bath and allowed to cool at least 20 min. Succinyl chloride (11.7 mL, 16.4 g, 106 mmol) was then added dropwise via syringe, slowly, over 50 min to control the resulting exotherm, with the first 1 mL added over 15 min, the next 3 mL over the next 15 min, and the remainder over 20 min. The reaction mixture turned from a yellow suspension to a white suspension, usually by the end of the addition but always within a few hours after addition is complete. The reaction was stirred under N_2 overnight (16−24 h) at room temperature. Allowing the flask to stir longer has no known deleterious effect. The slurry was allowed to settle for 1−2 h, vacuum

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filtered through qualitative filter paper on a large Buchner funnel, rinsed with additional THF, and dried under vacuum (0.06 mmHg) to yield a white solid (14.4489 g, 45.7% yield; 12.365 g, 39.1% yield) accounting for the THF present. Yields range from 30% to 46%, not accounting for residual THF, which is usually present in about 1.6 equiv after drying.[10]

Large Scale. A five-neck 22 L jacketed flask with a drain port was equipped with an overhead stirrer, a condenser, a baffle, a thermocouple, and a septum. The flask was charged with 2 L of THF followed by addition of the azine (**1**) (179.9 g, 607.2 mmol) under air. An additional 2.4 L of THF (total volume 4.4 L) were used to rinse the azine into the reactor. The mixture was stirred (at 160 rpm) under nitrogen for 18 h to remove oxygen. The jacket temperature was set to −10 °C, and the solution, −8 °C. To the flask was added 1,2-bis(phosphino)benzene (43.02 g, 296.7 mmol) via syringe. ***Caution:*** *1,2-Bis(phosphino)benzene is pyrophoric, and appropriate air-free handling techniques must be used!* The syringe was rinsed with approximately 10 mL of degassed THF. Succinyl chloride (100 mL, 140.7 g, 897.5 mmol) was added via syringe at a rate controlled by a syringe pump, targeting 25.0 mL/h (actual 28.6 mL/h, 3.5 h addition) to control the exotherm. After 1 h, the solution had lightened in color and increased in temperature by 2 °C (to −6 °C). After addition, the agitation rate was increased to 267 rpm to rinse material from the sides of the flask for 1 h before returning to 150 rpm. The chiller was then turned off to allow the mixture to stir and reach room temperature overnight (18 h). The solution was drained into a 22 L recovery flask, and the reactor was rinsed with 500 mL of THF to remove material. The product was isolated by suction filtration, rinsing with 1.6 L of THF, and dried in a vacuum oven (90 mmHg) at 40 °C overnight to yield (*rac*)-tetra-acid (**2**) (105.2 g, 39.5% crude yield, 35% yield accounting for THF present, 27.0% overall accounting for potency).

Spectral data are consistent with compound **4** reported below.

*Isolation of Diastereomeric Salt (**3**) by Classical Resolution with Pseudoephedrine.*[11] (*rac*)-Tetra-acid (**2**) (9.9987 g, 67.6% potent, 7.52 mmol) and (*R*,*R*)- pseudoephedrine (7.3528 g, 44.500 mmol) were combined in a 1 L Erlenmeyer flask. A volume of 434 mL (40 mg/mL total concentration) of 5% H_2O in MeCN was added, and the mixture was heated in a warm water bath at 55 °C and swirled until a clear yellow solution formed. Once the solution was fully homogeneous, it was allowed to stand at 55 °C with occasional swirling for 1 h. Then, the heater to the water bath was switched off, and the solution was allowed to cool undisturbed to room temperature overnight (16 h). Clumps of crystals formed overnight (see Figure S1 in SI for picture) and were isolated by decanting the mother liquor into a second 1 L Erlenmeyer flask followed by rinsing the solids with 5% H_2O in MeCN that was cooled to 0 °C (3 × 10 mL). The crystals were dried under a gentle stream of N_2 and transferred to a beaker[12] to yield a first crop of (*S*,*S*)-tetra-acid·4 (*R*,*R*)-pseudoephedrine salt (**3**) (5.504 g, 93.8% yield) as white crystals. The solvent from the washings was removed by rotary evaporation, and the residual solids were dissolved in the mother liquor. The mother liquor was placed in a refrigerator at 5 °C to stand for an additional day, during which a second batch of smaller, discrete crystals form. The mother liquor was again decanted, and the crystals were washed with cold (0 °C) 5% H_2O in MeCN (3 × 10 mL) to yield an additional 0.3565 g (6.08% yield) of (*S*,*S*)-tetra-acid·4 (*R*,*R*)-pseudoephedrine salt (**3**) after drying and transferring to a second beaker. A large amount of solid (approximately 100 mg) was dissolved in CD_3OD for NMR. By NMR, only one diastereomer is observed for each crop. The NMR sample is recycled into the next step.

^{1}H NMR (400 MHz, MeOD) δ 7.63 (d, J = 7.7 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.39−7.27 (m, 24H), 7.20 (m, 4H), 7.00 (m, 6H), 6.83 (t, J = 7.7 Hz, 2H), 6.47 (d, J = 7.9 Hz, 2H), 6.36 (s, 2H), 4.47 (d, J = 9.4 Hz, 4H), 3.17 (dq, J = 10.0, 6.6 Hz, 4H), 3.06 (td, J = 15.9, 4.9 Hz, 2H), 2.90 (td, J = 15.8, 5.1 Hz, 2H), 2.63−2.56 (m, 2H), 2.54 (s, 12H), 2.42 (dd, J = 16.2, 4.8 Hz, 2H), 0.94 (d, J = 6.6 Hz, 12H).

^{13}C NMR (126 MHz, MeOD) δ 177.2, 174.1, 171.0, 168.3, 143.3, 142.4, 139.4, 137.1, 136.3, 133.0, 131.0, 130.8, 130.0, 129.8, 129.6, 129.3, 128.4, 128.2, 127.0, 126.8, 75.7, 62.4, 62.2, 62.1, 61.8, 61.0, 31.1, 30.6, 30.4, 13.0.

^{31}P NMR (162 MHz, MeOD) δ 2.6 (the shift may vary between 0 and 5 ppm based on concentration).

*Isolation of Free (S,S) Tetra-acid (**2**).* (*S*,*S*)-Tetra-acid·4 (*R*,*R*)-pseudoephedrine salt (**3**) (5.861 g, 3.664 mmol) was dissolved in a minimal amount of methanol, adding in the NMR samples in CD_3OD used to check diastereopurity. This solution was acidified with 3 M HCl to form a white slurry. The slurry was vacuum filtered through qualitative filter paper two times, washed with water (3 × 15 mL), and dried under vacuum (0.050 mmHg) to yield a white solid (3.1856 g, 93.3% potent, 87.9% yield). The filtrate was kept for recovery of the (*R*,*R*)-pseudoephedrine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.52 (s, 3H), 8.05−7.97 (m, 2H), 7.68−7.59 (m, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.40 (dd, J = 6.3, 2.7 Hz, 2H), 7.29−7.17 (m, 4H), 7.15 (s, 2H), 7.12−7.06 (m, 2H), 7.04 (d, J = 7.8 Hz, 2H), 6.88 (ddt, J = 10.4, 7.3, 3.8 Hz, 4H), 6.54−6.44 (m, 2H), 2.86 (td, J = 16.1, 15.0, 7.0 Hz, 2H), 2.36 (qd, J = 16.0, 14.4, 5.7 Hz, 6H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 168.0, 167.6, 167.4, 165.2, 141.6, 141.2, 140.1, 139.1, 133.3, 131.5, 131.4, 131.3, 131.2, 130.2, 129.5, 129.0, 128.8, 128.0, 127.6, 127.2, 127.0, 126.7, 126.1, 58.0, 54.8, 29.5, 29.5.

^{31}P NMR (162 MHz, DMSO) δ 4.7.

*Recovery of Free (R,R)-Enriched Tetra-acid (**2**).* The mother liquor and the washings from the second recrystallization were combined, and the solvent was removed by rotary evaporation (3.2 mmHg) to yield pale yellow solids of (*R*,*R*)-enriched tetra-acid and (*R*,*R*)-pseudoephedrine. These solids were dissolved in a minimal amount of methanol. The resulting solution was acidified with 3 M HCl to yield a white slurry. The slurry was vacuum filtered through qualitative filter paper two times, washed with water (at least 5 × 15 mL, more may be required to removed residual pseudoephedrine), and dried under vacuum (0.050 mmHg) to yield (*R*,*R*)-enriched tetra-acid (**2**) as an off-white solid (4.7230 g). The filtrate was kept for recovery of the (*R*,*R*)-pseudoephedrine.

Spectral data are consistent with compound **2** reported above.

Recovery of (R,R)-Pseudoephedrine. The filtrates from the isolation of each enantiomer of tetra-acid were combined, and the solution was made basic by addition of solid NaOH until the solution pH exceeded 11, resulting in the formation of white solids. The slurry (approximately 300 mL in volume) was transferred to a 1 L separatory funnel and extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed by rotary evaporation to yield (*R*,*R*)-pseudoephedrine (6.641 g, 97.1% potent, 87.7% recovery).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.30 (m, 4H), 7.26 (m, 1H), 4.17 (d, J = 8.2 Hz, 1H), 2.81 (br s, 1H), 2.60 (dq, J = 8.0, 6.4 Hz, 1H), 2.41 (s, 3H), 0.90 (d, J = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 128.3, 127.7, 127.1, 77.7, 61.4, 33.6, 15.7.

*Synthesis of (S,S,S)-Bisdiazaphos-SPE (**5**).* A 100 mL round-bottom Schlenk flask equipped with a magnetic stir bar was cooled under vacuum, refilled with nitrogen, charged with (*S*,*S*)-tetra-acid (**2**) (2.0045 g, 95.4% potent, 2.128 mmol),[13] and sealed with a septum. The flask was evacuated and filled with nitrogen (3×). To the flask was added EtOAc (40 mL, 1 mL/35 mg tetra-acid) via syringe. The slurry was stirred, *N*,*N*-diisopropylethylamine (2.93 mL, 16.8 mmol) was added via syringe, followed by (*S*)-(α)-methylbenzylamine (4.44 mL, 34.4 mmol) which was also added via syringe. T3P solution (10.0 mL, 16.8 mmol, 50 wt % in ethyl acetate) was added, and the slurry began to dissolve. The flask was equipped with a reflux condenser and transferred to an oil bath at 70 °C and allowed to stir for 48 h. The reaction was removed from the oil bath and allowed to cool before transferring to a 1 L separatory funnel. The solution was diluted by the addition of 250 mL EtOAc and quenched by the addition of H_2O (200 mL). The aqueous layer was removed, and the solution was further washed with 1 M HCl (2 × 200 mL) and H_2O (200 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed by rotatory evaporation (3.2 mmHg) to obtain crude (*S*,*S*,*S*)-Bisdiazaphos-SPE

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(**5**) and T3P byproducts as a pale yellow solid (3.308 g, (68.7% potent, 81.4% potency adjusted yield).

Spectral data are consistent with compound **6** reported below.

*Isolation of Purified (S,S,S)-Bisdiazaphos-SPE (**6**) as Acetone Solvate.* The isolated material from the coupling reaction (3.308 g) was retained in a 250 mL round-bottom flask where it was slurried by the addition of acetone (33.1 mL, 10 mL/g) and placed in a freezer at −5 °C overnight. Solids precipitated from the slurry were rinsed with cold (0 °C) acetone (2 × 15 mL) to yield a white solid. The solid was dried under vacuum (0.03 mmHg) to obtain the desired (*S,S,S*)-BDP ligand (**6**) (2.1904 g, 90.1% potent, 86.8% recovery).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, J = 8.3 Hz, 2H), 7.64 (dd, J = 7.4, 1.5 Hz, 2H), 7.49 (d, J = 7.2 Hz, 4H), 7.35−7.16 (m, 20H), 7.07 (dd, J = 5.5, 3.3 Hz, 2H), 6.95 (t, J = 9.2 Hz, 2H), 6.85 (d, J = 7.6 Hz, 2H), 6.80 (dd, J = 11.0, 5.1 Hz, 4H), 6.67 (dt, J = 14.8, 7.3 Hz, 4H), 6.28 (t, J = 7.1 Hz, 2H), 6.20 (s, 2H), 5.87 (d, J = 7.9 Hz, 2H), 5.46 (p, J = 7.0 Hz, 2H), 4.97 (p, J = 7.0 Hz, 2H), 2.68−2.52 (m, 4H), 2.50−2.40 (m, 4H), 1.58 (d, J = 7.0 Hz, 6H), 1.20 (d, J = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 166.7, 165.6, 144.2, 143.0, 137.9, 136.8, 134.3, 134.1, 133.0, 131.5, 130.4, 130.3, 130.2, 129.2, 129.0, 128.8, 128.4, 128.0, 127.3, 127.1, 126.8, 126.6, 125.4, 124.7, 57.6, 54.6, 49.8, 49.3, 29.4, 29.1, 23.2, 22.0.

^{31}P NMR (162 MHz, $CDCl_3$) δ 6.9.

HRMS (ESI-Orbitrap) calcd for $C_{78}H_{73}N_8O_8P_2$ $(M + H)^+$ 1311.5021, found 1311.5027.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01915.

Crystallographic data (CIF)

Pictures of crystals, potency determination, NMR investigation of the azine, X-ray data, and copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040−5042. (b) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553−4556. (c) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027−14029. (d) Watkins, A. L.; Landis, C. R. *Org. Lett.* **2011**, *13*, 164−167. (e) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 1180−1182. (f) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 2572−2575. (g) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6757−6761. (h) Abrams, M. L.; Foarta, F.; Landis, C. R. *J. Am. Chem. Soc.* **2014**, *136*, 14583−14588.

(2) Wong, G. W.; Adint, T. T.; Landis, C. R. *Org. Synth.* **2012**, *89*, 243−254.

(3) Adint, T. T.; Wong, G. W.; Landis, C. R. *J. Org. Chem.* **2013**, *78*, 4231−4238.

(4) Adint, T. T.; Landis, C. R. *J. Am. Chem. Soc.* **2014**, *136*, 7943−7953.

(5) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792−11793.

(6) See SI for a ^{31}P NMR of the residual material.

(7) See SI for details of comparison to authentic sample and derivitization.

(8) See SI for potency determination.

(9) The material contains 5.5 wt% acetone by mass, which was not removed under high-vac (0.06 mmHg, 1 h), and 4.7% of unidentified material, thought to be T3P degradation byproducts. A second recrystallization reduced the amount of byproduct in the ^{31}P NMR from 3.6% to 1.7%. This byproduct has not been observed to affect hydroformylation.

(10) The tetra-acid **2** has been stored as a solid under air for up to 18 months without oxidation. The oxidized product has a ^{31}P NMR shift of 55.78 ppm (DMSO-d_6).

(11) Other chiral amines were evaluated as alternatives for the resolution of diastereomers including strychnine, quinine, (*R*)-(+)-α-methylbenzylamine, (1*S*,2*S*,3*S*,5*R*)-(+)-isocampheylamine, (−)-nicotine, (*R*)-(−)-1-amino-2-propanol, (1*S*,2*S*)-(+)-*trans*-1-amino-2-indanol, (*S*)-(+)-2-pyrrolidinemethanol, and (1*R*,2*R*)-pseudoephenamine; however, these compounds were not suitable for the separation.

(12) Small amounts of material from the mother liquor remain after washing which may be less diastereomerically pure than the crystals. Transferring the crystals to a second container leads to diastereomerically pure solids. Though it was not observed with the optimized conditions, material of low *de* can be recombined with the mother liquor, followed by solvent removal *in vacuo*, and redissolved and resubjected to the resolution to yield diastereomerically pure solids.

(13) The tetra-acid contains residual water after drying under vacuum. Equivalents of tetra-acid are calculated based on the water-adjusted potency, in this case 96.5 or 2.151 mmol. The solid was determined to contain 3.5% H_2O (0.0710 g, 3.93 mmol) by NMR. This water reacts with T3P, so an additional amount of T3P equimolar to H_2O present in the tetra-acid is added. An additional amount of *N,N*-diisopropylethylamine equimolar to water is used as well.

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