Scalable and chromatography-free synthesis of 2-(2-formylalkyl)arenecarboxylic acid derivatives through the supramolecularly controlled hydroformylation of vinylarene-2-carboxylic acids

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This protocol describes how to prepare 2-(2-formylalkyl)-arenecarboxylic acid derivatives, common building blocks for the synthesis of various valuable chemicals (e.g., anti-obesity and Alzheimer's disease treatment pharmaceuticals), by using the fully regioselective hydroformylation of vinyl arene derivatives. This catalytic reaction proceeds cleanly with 100% regioselectivity and chemoselectivity. The procedure is reliably scalable and can be efficiently conducted on a multigram scale. The analytically pure product is easily isolated with a nearly quantitative yield by using a simple acid-base extraction workup and avoids any tedious chromatography. This protocol details the synthesis of a bisphosphite ligand (L1) that is a pivotal element of the catalytic system used, $Rh(acac)(CO)_2$ with ligand L1, starting from commercial building blocks. The protocol also describes a general procedure for the preparative hydroformylation of vinylarene-2-carboxylic acid derivatives to 2-formylalkylarene products, providing a representative example for the hydroformylation of 2-vinylbenzoic acid (1a) to 2-(3-oxopropane)-benzoic acid (2a). The synthesis of L1 (six chemical reactions) uses 2-nitrophenylhydrazine, 4-benzyloxybenzoylchloride and (S)-binol, and takes 5–7 working days. The actual hydroformylation reaction of each vinyl arene derivative takes ~4 h of active effort over a period of 1–3 d.

INTRODUCTION

Beta-aryl aldehydes represent a class of common intermediates in the synthesis of different important organic structures, including various fine chemicals such as pharmaceuticals, agrochemicals and other materials[1,2]. Therefore, easy access to a series of derivatives is essential, for instance, in the development of new or improved drugs. In principle, hydroformylation of abundant vinyl arenes could provide this class of compounds by introducing an aldehyde group to a carbon-carbon double bond with 100% atom economy[3]. However, the reaction typically leads to only a small percent of the beta-aldehyde product, alongside the main product, the alpha-aldehyde. Formation of the latter is promoted by the additional π-benzyl interactions with the adjacent aromatic ring[4]. Despite intensive research in the field of hydroformylation, there are almost no catalytic systems that can effectively surmount this 'natural' selectivity for a wide scope of substrates. Some catalysts that show selective conversion have been reported for styrene but not for important analogs thereof[2,5,6]. In practical synthesis, beta-aryl aldehyde intermediates are typically prepared by alternative routes, which generally involve rather sophisticated and tedious stoichiometric reactions burdened by waste production[7–9]. The development of general beta-selective hydroformylation protocols for important classes of vinyl arenes enables the use of clean and short synthetic routes for the formation of these valuable building blocks.

Inspired by the effectiveness of enzymes, for which noncovalent substrate preorganization has an important role[10], and on the basis of our previous studies on the regioselective hydroformylation of olefins[11–13], we devised a catalytic system for the beta-regioselective hydroformylation of an important class of vinyl arenes: vinylarene-2-carboxylic acids[14]. The beta-aldehyde products of this class of vinyl arenes are common building blocks for the synthesis of various valuable chemicals[15–21], for instance, putative anti-obesity[21] pharmaceuticals and ones for treatment of Alzheimer's disease[18]. The developed catalyst provides the beta-aldehyde products with 100% regioselectivity and chemoselectivity, which can be easily and nearly quantitatively isolated with a simple acid-base extraction work-up. The procedure is scalable as demonstrated on a 5-g scale. The catalyst operates under mild conditions and can be used for a wide scope of substrates, including those with the most challenging 1,2-disubstituted carbon-carbon double bond (**Fig. 1**). This catalytic system opens unprecedented routes for the formation of these valuable beta-aldehyde intermediates from simple building blocks by using only green reactions, especially when combined with a clean catalytic technology that allows the introduction of vinyl groups onto aromatic substrates by aromatic C-H activation routes[22,23] and selective C-H alkylation of alkenes[24]. This process is limited to substrates that have a carboxylate group (or an alternative anionic functional group) close to the vinyl group. The introduction and possible removal of this group may require additional reaction steps.

Example procedures

This protocol details the synthesis of the bisphosphite ligand **L1**—the pivotal element of the catalytic system (i.e., $Rh(acac)(CO)_2$ with ligand **L1**) for the title reaction—starting from commercially available building blocks (**Fig. 2**), utilizing the previously described synthesis of bis(nitroindolyl)propane **3** (ref. 25). Although the procedure is effective, can be scaled up or down without any difficulties and can be performed on a multigram scale, it

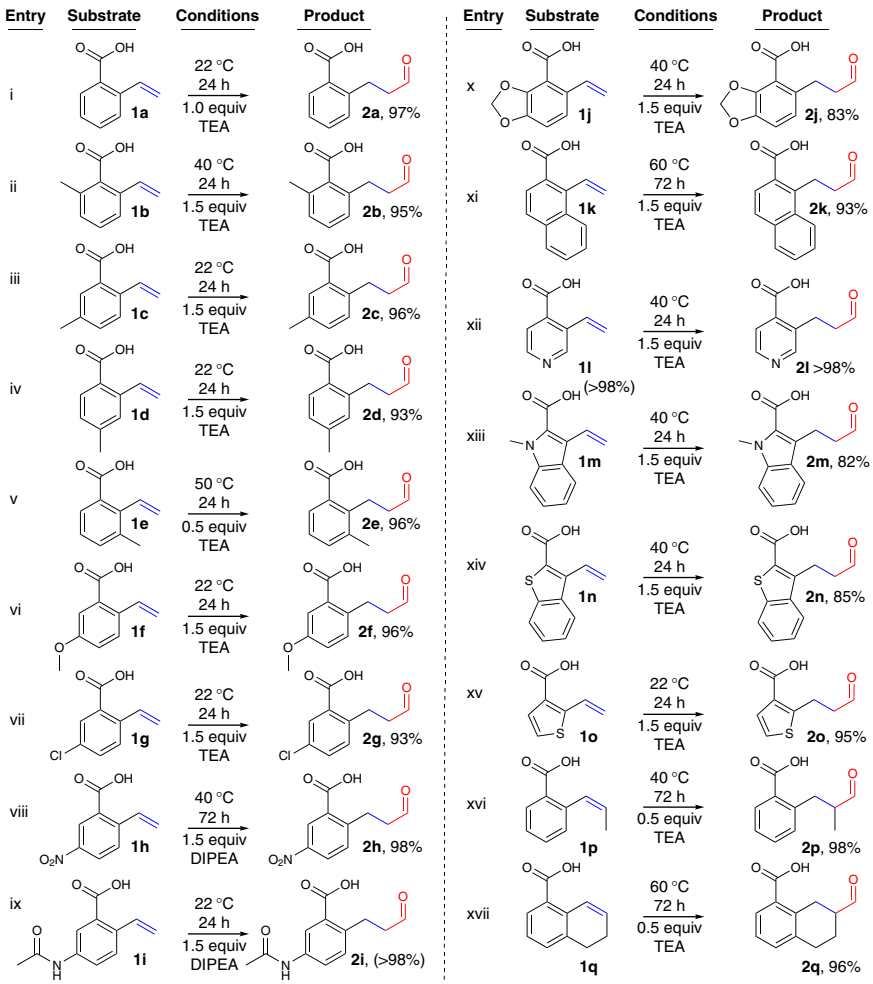

Figure 1 | Examples of the hydroformylation of 2-vinylarenecarboxylic acids **1a–q** to 2-(2-formylalkyl) arenecarboxylic acid derivatives **2a–q**. TEA, triethylamine; DIPEA, N,N-diisopropylethylamine. Representative isolated yields for reactions conducted on a 0.3–0.8 mmol scale; isolated yields may vary (± 5%) because of losses during the isolation. Values in parentheses indicate NMR spectroscopy yield. Full conversion of the starting material was observed in all cases, except for entries xi and xvi, in which conversion was 95% and 98%, respectively. No side products were observed.

includes several steps that require special care (Steps 27–33, and Step 4 when performed on a multigram scale).

In addition to the preparation of **L1**, we describe a representative protocol for the catalytic preparation of *2*-(2-formyl alkyl)arenecarboxylic acids using hydroformylation of 2-vinylbenzoic acid (**1a**) to 2-(3-oxopropyl)benzoic acid (**2a**) as an example (**Fig. 1**, Entry i). The procedure is general for different vinylarene-2-carboxylic acids and works well for various derivatives (except for 2-vinyl-3-furoic acid)[14]; yet, in some cases the temperature, reaction time or catalyst loading may need to be optimized to accomplish the reaction (**Fig. 1**).

MATERIALS

REAGENTS

! CAUTION All chemicals must be handled with care as many of them are potentially hazardous; consult the safety documentation for each chemical. Wear personal protective clothing (lab coat, suitable gloves, safety glasses and so on); reaction setup should be carried out in a well-ventilated fume hood; while handling syngas (CO-H_2 mixture), use a personal CO detector and remove all possible ignition sources.

- 2-Nitrophenylhydrazine 97%, moistened with ~30% (wt/wt) water (Acros Organics, cat. no. 128830100)
- Propionaldehyde >97% (any commercial supplier)
- Palladium on activated charcoal, 10% Pd basis (Sigma-Aldrich, cat. no. 75990-50G)
- 4-Benzyloxybenzoylchloride 95% (Sigma-Aldrich, cat. no. 682861-5G)
- (S)-(-)-1,1′-Bi-2-naphthol, 99%+ (any commercial supplier)
- Phosphorus trichloride, 99% (PCl_3; any commercial supplier)
- 2-Vinylbenzoic acid, 96% (Alfa Aesar, cat. no. H31723)
- (Acetylacetonato)dicarbonylrhodium(I), $Rh(acac)(CO)_2$ 98% (any commercial supplier)
- Sodium biscarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), magnesium sulfate ($MgSO_4$) anhydrous (any commercial supplier)
- Hydrochloric acid (HCl), for analysis and for fuming, use 37% solution in water (Acros Organics, cat. no. 124630010)
- Celite 512 medium (Sigma-Aldrich, cat. no. 22152-1KG)
- Methanol, ethanol, tetrahydrofuran (THF), toluene, ethyl acetate, dichloromethane (DCM), chloroform, 1,2-dichloroethane ($C_2H_4Cl_2$), cyclohexane (C_6H_{12}), acetone, triethylamine (TEA)—all of analytical grade (any commercial supplier)

EQUIPMENT

- Argon-vacuum dual manifold
- Vacuum pump
- Laboratory oven
- Bunsen burner or heat gun
- Magnetic stirrer with a heating plate
- Oil bath
- Teflon-coated stirring bars
- Analytical weighing balance
- Hemispherical Dewar flasks
- Rotary evaporator with water bath
- Ultrasonic bath
- Stainless steel autoclave
- High-pressure syngas manifold
- Access to analytical facilities (NMR, MS and elemental analysis (EA))
- Solvent purifier (MBraun, MB-SPS) and/or distillation setup
- Schlenk flasks
- Round-bottomed flasks
- Reflux condenser
- Addition funnel
- Separatory funnel
- Rubber septae
- Disposable syringes and needles
- Stainless steel needles
- Spatulas
- Weighing funnels

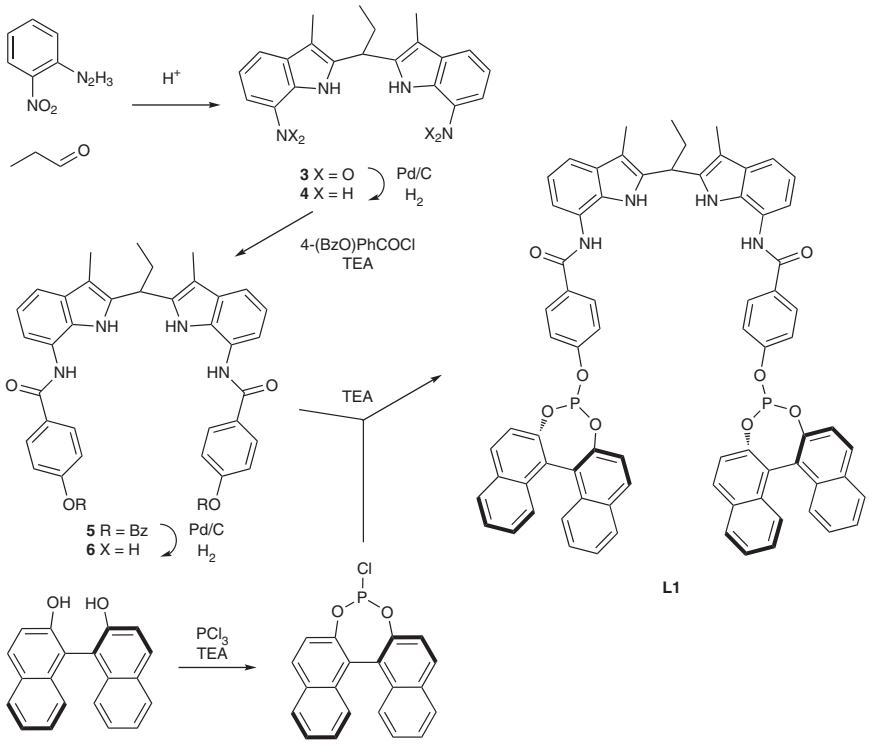

Figure 2 | Synthesis of ligand **L1** from commercial 2-nitrophenylhydrazine and (S)-binol. TEA, triethylamine; Bz, benzyl.

- Silica thin-layer chromatography (TLC) plates (silica gel 60 F_{254}, Merck) and capillary spotters
- TLC developing chamber
- Silica gel for preparative column chromatography (silica gel, 40–63 µm (230–400 mesh))
- Glass column for preparative flash chromatography
- Test tubes
- Beakers
- Liquid nitrogen and dry ice
- Erlenmeyer flask
- Magnetic stirring bar

REAGENT SETUP

PCl_3 Commercial PCl_3 should be distilled and stored under inert conditions in a Strauss flask (as such it can be stored for several months).

THF, toluene, cyclohexane and DCM These solvents should be purified and dried in a solvent purifier directly before use. Alternatively, the solvents can be used if they are freshly dried and distilled: THF and cyclohexane from sodium benzophenone ketyl; CH_2Cl_2 from CaH_2; and toluene from sodium under nitrogen.

Triethylamine Purify and dry freshly before use by distillation from KOH pellets under nitrogen.

EQUIPMENT SETUP

Reaction flask for moisture-sensitive reactions The reaction Schlenk flask should be dried overnight in the laboratory oven (>140 °C), then equipped with a magnetic stirring bar, flame-dried under reduced pressure on a vacuum-argon manifold, cooled to room temperature (~30–40 °C), backfilled with argon (at least three vacuum-argon cycles), and it should stay connected to an argon line with a slight overpressure (~1 kPa) of inert gas.

PROCEDURE

Preparation of 1,1-bis-(-3-methyl-7-nitro-1H-indol-2-yl)-propane (3) ● TIMING 1 d

1| Charge a 1-liter round-bottomed two-necked flask with 60 g of 2-nitrophenylhydrazine (moistened with 30% water (wt/wt), as received from Acros Organics; 1.0 equiv.). Add to it 80 ml of propionaldehyde (4.0 equiv.), 2 ml of acetic acid and 500 ml of ethanol. Place the flask in an oil bath with a thermocouple temperature sensor. Fix the reflux condenser, block the other neck with a glass stopper and heat the oil bath to 95 °C for 2 h.

2| Once the flask has cooled down close to room temperature, remove all volatiles by using a rotary evaporator (the water bath at 40–50 °C, timing ~30 min).

3| Add 600 ml of 37% aqueous solution of HCl to the flask and place it in an ultrasonic bath for 1 h (or until a homogenous suspension is obtained).

! CAUTION $HCl_{(aq)}$ is highly corrosive, and its vapors irritate the eyes and throat. Carry out Steps 3–5 in a well-vented fume hood.

4| Place the flask in an oil bath with a thermocouple temperature sensor. Fix the reflux condenser and the addition funnel. Charge the addition funnel with 80 ml of propionaldehyde (4.0 equiv.). Slowly heat the oil bath to 105 °C for 1 h; during this time add propionaldehyde dropwise from the addition funnel, and stir the reaction mixture vigorously.

! CAUTION The reaction is highly exothermic. Observe the reaction mixture and remove the heating bath tentatively if vigorous refluxing occurs.

5| After cooling, transfer the reaction mixture to a 5-liter beaker containing 1 liter of water, and add 500 ml of chloroform to it. Place the beaker in a water/ice cooling bath. Carefully and slowly add Na_2CO_3 (~0.5 g at a time), while vigorously stirring, until basic pH (pH >7) is achieved.

! CAUTION Heat and CO_2 are released during Na_2CO_3 addition; thus the slow addition, cooling and vigorous stirring are essential here. Controlling temperature of the mixture is advised.

6| Separate the organic phase and extract the aqueous phase twice with 500 ml of chloroform by using a separator funnel.

7| Combine the organic phases in an Erlenmeyer flask, add 150 g of anhydrous $MgSO_4$, stir for ~10 min and then filter the mixture into a round-bottomed flask. Remove all volatiles by using a rotary evaporator (the water bath at 40–50 °C, timing ~1 h).

8| Add 50 ml of 1,2-dichloroethane and heat the mixture until all solids dissolve. Allow the resulting solution to cool down to room temperature and leave it for another 30 min to let the product precipitate. Collect the precipitated product by using a frit funnel (porosity grade 3) and wash it with 150 ml of cooled methanol and 150 ml of hexane.
? TROUBLESHOOTING

9| Dry the orange solid under vacuum. Check the purity of **3** by using NMR spectroscopy or by determining the melting point (see ANTICIPATED RESULTS).
? TROUBLESHOOTING
■ **PAUSE POINT** Compound **3** can be stored indefinitely at room temperature under air.

Preparation of bis-(4-(benzyloxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane) (5) ● **TIMING 2 d**
10| Suspend 3.09 g of dinitro compound **3** (1.0 equiv.) in 130 ml of methanol in a 500-ml round-bottomed Schlenk flask. Add 0.8 g of 10% palladium on charcoal to it.
! CAUTION Palladium on charcoal can ignite solvent vapors in the presence of oxygen. Therefore, the flask should be backfilled and kept under positive pressure of an inert gas.

11| Fix a balloon filled with hydrogen (~5 liters) on the flask. Flush the flask with ~2 liters of hydrogen from the balloon, and leave the balloon on the flask. Vigorously stir the mixture for 1 h.
! CAUTION Hydrogen is highly flammable. Work in a well-vented fume hood. Remove all possible ignition sources.

12| Check for the completion of the reaction with TLC analysis on silica TLC plates. The retardation factors (R_f) of the substrate, the intermediate and the product in hexanes/ethyl acetate (7:3 (vol:vol)) are ~0.7 (yellow spot), ~0.15 (yellow spot that slowly turns brown under air) and ~0.1 (colorless spot that slowly turns brown under air), respectively.
? TROUBLESHOOTING

13| Filter the mixture through a bed of Celite into a 500-ml round-bottomed Schlenk flask. Wash the Celite thoroughly with methanol. Remove all volatiles by using a rotary evaporator (water bath at up to 40 °C, for ~30 min).
! CAUTION It is essential to remove all methanol from the reaction mixture, as it can react with the acid chloride in the next step. Prolonged (~20 min) drying under vacuum is advised. Alternatively, traces of methanol can be removed azeotropically by dissolving the solid residue in small volume of chloroform (~15 ml) followed by its evaporation with a rotary evaporator (the water bath at up to 40 °C, timing ~10 min).

14| Charge the flask with a magnetic stirring bar, seal it with a rubber septum and backfill it with argon (at least three vacuum-argon cycles). Add 100 ml of dry CH_2Cl_2 and 8.85 ml of dry TEA to it.

15| Dissolve 4.86g of 4-(benzyloxy) benzoyl chloride (2.5 equiv.) in 30 ml of dry CH_2Cl_2 in another Schlenk flask under argon. By using a syringe, add the solution dropwise to the main reaction mixture while stirring, and continue stirring overnight (~12 h).
! CAUTION 4-(benzyloxy)benzoyl chloride is sensitive to moisture. Air and moisture should be prevented from entering the reaction flask. Therefore, the reaction flask should be kept under positive argon pressure.

16| Wash the reaction mixture twice with 100 ml of saturated water solution of $NaHCO_3$ and once with 100 ml of water by using a separator funnel.

17| Transfer the organic phases into an Erlenmeyer flask, add 20 g of anhydrous $MgSO_4$ and stir for ~10 min. Filter the mixture into a round-bottomed flask. Remove all volatiles by using a rotary evaporator (the water bath at 40 °C, timing ~15 min).

18| Purify the crude product by flash chromatography on 120 g of silica gel by using a CH_2Cl_2: methanol (99:1 (vol:vol)) mixture as an eluent.

19| Collect the product containing fractions in a round-bottomed flask and remove the solvents by using a rotary evaporator (the water bath at 40–50 °C, timing ~30 min). The product should be the first eluted compound, unless methyl 4-(benzyloxy)benzoate formed, owing to the presence of traces of methanol in the reaction mixture. In that case, methyl 4-(benzyloxy)benzoate elutes first, followed by the product.

20| Dry the solid under vacuum. Check the purity of **5** by using NMR spectroscopy.
■ **PAUSE POINT** Compound **5** can be stored under argon for months without a noticeable loss of purity.

Preparation of bis-(4-(hydroxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane) (6) ● **TIMING 1 d**
21| Dissolve 5.40 g of compound **5** in 120 ml of a methanol:THF (1:3 (vol:vol)) mixture in a 500-ml round-bottomed Schlenk flask. Add 1.68 g of 10% palladium on charcoal to it.
! **CAUTION** Palladium on charcoal can ignite solvent vapors in the presence of oxygen. Therefore, the flask should be filled and kept under positive pressure of an inert gas.

22| Fix a balloon filled with hydrogen (~5 liters) on the flask. Flush the flask with ~2 liters of hydrogen from the balloon and leave the balloon on the flask. Place the flask in an oil bath with a thermocouple temperature sensor, and heat the oil bath to 40 °C. Vigorously stir the mixture overnight (~12 h).
! **CAUTION** Hydrogen is highly flammable. Work in a well-vented fume hood. Remove all possible ignition sources.

23| Check for the completion of the reaction with TLC analysis on silica TLC plates. The retardation factors (R_f) of the substrate, intermediate and the product in CH_2Cl_2/methanol (95:5 (vol:vol)) are ~0.7, ~0.3 and ~0.25, respectively.
? TROUBLESHOOTING

24| Filter the mixture through a bed of Celite into a round-bottomed flask. Wash the Celite thoroughly with methanol and THF (100 ml of each). Remove all volatiles by using a rotary evaporator (the water bath at 40–50 °C, timing ~30 min).

25| Dissolve/suspend the solids in 10 ml of CH_2Cl_2. Add 200 ml of hexane to precipitate the product. Place the flask in an ultrasonic bath for 15 min. Collect the precipitated product by using a frit funnel (porosity grade 3).

26| Dry the solid under vacuum. Check the purity of **6** by using NMR spectroscopy and elemental analysis.
■ **PAUSE POINT** Compound **6** can be stored under argon for months without noticeable loss of purity.

Preparation of (S)-1,1′-Binaphthyl-2,2-diyl phosphorochloridate, (S)-binol-PCl (7) ● **TIMING 4 h**
▲ **CRITICAL** All glassware should be oven-dried and flame-dried under vacuum. All solvents and reagents should be dry and degassed. Air and moisture should be prevented from entering the reaction flask. Therefore, the reaction flask should always be kept under positive argon pressure (or vacuum).
▲ **CRITICAL** (S)-binol-PCl should be prepared and used immediately for coupling with compound **6** (Steps 30–33).

27| Dissolve/suspend 1.14 g of (S)-(-)-1,1′-bi-2-naphthol ((S)-binol; 2 equiv.) in 10 ml of dry toluene in a 150-ml round-bottomed Schlenk flask sealed with a rubber septum. Evaporate the volatiles under vacuum by using the argon-vacuum dual manifold. Dissolve the solid in 20 ml of dry and degassed THF.

28| Charge another 150-ml round-bottomed Schlenk flask, sealed with a rubber septum, with 20 ml of dry and degassed THF and 1.1 ml of TEA. Cool the solution to –78 °C by using a dry ice/acetone cooling bath in a hemispherical Dewar flask. Add 0.40 ml of PCl_3 (2.3 equiv.) dropwise to the solution. Add dropwise the solution of (S)-binol in THF via a septum by using a syringe, and continue stirring for 20 min at –78 °C. Remove the cooling bath, let the reaction mixture warm up to room temperature, and continue stirring for another 45 min in room temperature. Evaporate the volatiles under vacuum by using the argon-vacuum dual manifold. Add 10 ml of dry and degassed toluene, and again evaporate the volatiles under vacuum by using the argon-vacuum dual manifold. Dissolve/suspend the solids in 30 ml of dry and degassed THF.

29| Check the purity of **7** by using NMR spectroscopy. For this, transfer a small amount (~50 µl) of the solution to a dry NMR tube under argon by using a syringe and a Schlenk flask for NMR tubes, and dilute the sample with dry and degassed THF-h_8. Perform $^{31}P\{^1H\}$ NMR (unlocked) experiment: there should be only one singlet signal at ~177.9 p.p.m.
? TROUBLESHOOTING

Preparation of ligand L1 ● **TIMING 2 d**
▲ **CRITICAL** All glassware should be oven-dried and flame-dried under vacuum. All solvents and reagents should be dry and degassed. Air and moisture should be prevented from entering the reaction flask. Therefore, the reaction flask should be always kept under positive argon pressure (or vacuum).

30| Charge a 250-ml round-bottomed Schlenk flask with 1.14 g of compound **6**. Seal the flask with a rubber septum. Add 10 ml of dry and degassed toluene to the flask. Evaporate the volatiles under vacuum by using the argon-vacuum dual manifold.

Dissolve the solids in 20 ml of dry and degassed THF and 2.8 ml of TEA. Cool the solution to –78 °C by using a dry ice/acetone cooling bath in a hemispherical Dewar flask. Add dropwise the solution of freshly prepared (S)-binol-PCl **7** in THF through the septum with the help of a syringe, and continue stirring for 30 min. Remove the cooling bath and let the reaction mixture warm up to room temperature, and continue stirring overnight (~12 h) at room temperature.

31| Evaporate the volatiles under vacuum by using the argon-vacuum dual manifold. Add 20 ml of dry and degassed THF and 2 ml of TEA. Filter the suspension through a bed of oven-dried SiO_2 under argon by using a Schlenk filter funnel. Wash the SiO_2 bed with 20 ml of THF.
! CAUTION It is essential to perform the filtration and washing as fast as possible, as the product slowly decomposes on the silica gel.

32| Concentrate the combined organic fractions to ~10 ml volume by using the argon-vacuum dual manifold. Add 20 ml of dry and degassed cyclohexane. Evaporate the volatiles under vacuum by using the argon-vacuum dual manifold.

33| Dry the solid under vacuum. Check the purity of **L1** by using NMR spectroscopy and elemental analysis.
? TROUBLESHOOTING
■ **PAUSE POINT** Ligand **L1** can be stored under argon at –20 °C for months without noticeable loss of purity.

General procedure for the hydroformylation of vinylarene-2-carboxylic acids (1) to 2-(2-formylalkyl)arene-carboxylic acids (2)
34| Dissolve 1.0 equiv. of the corresponding vinylarene-2-carboxylic acid **1**, 0.5–1.5 equiv. of TEA, 0.01 equiv. $Rh(acac)(CO)_2$, 0.011 equiv. of ligand **L1** in dry and degassed CH_2Cl_2 (0.20 M) in a dry Schlenk flask sealed with a rubber septum.

35| Transfer the solution to a stainless-steel autoclave equipped with an oven-dried glass insert with a Teflon-coated stirring bar. Purge the autoclave three times with 20 bar of syngas ($CO:H_2$, 1:1 (mol:mol)) and then pressurize it to 20 bar pressure of syngas.
! CAUTION For safety purposes, the exhaust of the venting line should be placed high in the fume hood.

36| Heat the reaction up to the desired temperature by using the integrated heating system. Alternatively, place the autoclave in an oil bath with a thermocouple temperature sensor, and heat the oil bath to desired temperature for an appropriate reaction time while vigorously stirring the reaction mixture.
! CAUTION Syngas is highly toxic, poisonous and flammable. Work in a well-vented fume hood. Keep the sash down during all experiments. Remove all possible ignition sources. Use of a carbon monoxide personal detector is highly recommended.
▲ **CRITICAL STEP** The temperature of the oil bath and that of the solution inside the autoclave may differ (~5–15 °C) depending on the setup. Calibration is recommended.

37| Remove the heating bath. Cool down the reactor to almost room temperature (with the help of an ice-water cooling bath). Carefully remove the pressure of syngas.
! CAUTION For safety purposes, the exhaust of the venting line should be placed high in the fume hood.

38| Flush the autoclave with an inert gas (or air). Transfer the reaction mixture to a separator funnel, and dilute the mixture twice with CH_2Cl_2. Extract the product with an aqueous saturated solution of $NaHCO_3$ (three times with approximately one-third volume of the organic phase volume).

39| Neutralize the combined aqueous fractions with a 1 M aqueous solution of HCl. Extract the product with CH_2Cl_2 or with ethyl acetate (three times with a volume of the aqueous phase volume).

40| Add anhydrous $MgSO_4$ (1–2 g per 10 ml of solvents) to the combined organic fractions, stir for 10 min and filter the mixture into a round-bottomed flask. Remove all volatiles by using a rotary evaporator (the water bath at 40–50 °C).

41| Dry the solid under vacuum. Check the structure and purity of the desired product by using NMR spectroscopy and mass spectrometry.

Representative protocol for the catalytic preparation of 2-(3-oxopropane)-benzoic acid 2a ● TIMING 4 h of active effort over a 20-h period
42| Dissolve 4.44 g of 2-vinylbenzoic acid **1a** (1 equiv.), 4.15 ml of TEA (1.equiv.), 14 mg of $Rh(acac)(CO)_2$ (0.0025 equiv.) and 104 mg of ligand **L1** (0.00275 equiv.) in 96 ml of dry and degassed CH_2Cl_2 (0.20 M) in a dry Schlenk flask sealed with a rubber septum.

43| Transfer the solution to a stainless steel autoclave equipped with an oven-dried 250 ml-glass insert with a Teflon-coated stirring bar. Purge the autoclave three times with 20 bar of syngas ($CO:H_2$, 1:1 (mol:mol)) and then pressurize it to 20 bar of pressure of syngas. Place the autoclave in an oil bath with a thermocouple temperature sensor, and heat the oil bath to 40 °C for 16 h while vigorously stirring the reaction mixture.
! CAUTION Syngas is highly toxic, poisonous and flammable. Work in a well-vented fume hood. Keep the sash down during all experiments. Remove all possible ignition sources. The use of a carbon monoxide personal detector is highly recommended. For safety purposes, the exhaust of the venting line should be placed high in the fume hood.

44| Once the reactor has cooled down to room temperature with the help of an ice-water cooling bath, carefully remove the pressure of syngas. Flush the autoclave with an inert gas (or air). Transfer the reaction mixture to a separator funnel, and dilute it with 100 ml of CH_2Cl_2. Extract the product three times with 60 ml of an aqueous saturated solution of $NaHCO_3$.

45| Neutralize the combined aqueous fractions with a 1 M aqueous solution of HCl. Extract the product three times with 200 ml of CH_2Cl_2.

46| Add 60 g of anhydrous $MgSO_4$ to the combined organic fractions, stir for 10 min and filter the mixture into a round-bottomed flask. Remove all volatiles by using a rotary evaporator (the water bath at 40–50 °C, timing ~45 min).

47| Dry the solid under vacuum. Check the purity of the product by using NMR spectroscopy and elemental analysis.
? TROUBLESHOOTING

? TROUBLESHOOTING

Troubleshooting advice can be found in **Table 1**.

TABLE 1 | Troubleshooting table.

Step	Problem	Possible reason	Solution
8	Low yield of the product is obtained	Excess of 1,2-dichloroethane in the recrystallization	Repeat the purification using less amount of 1,2-dichloroethane
9	Impurities in the product are obtained	Precipitation of the product was too fast; amount of 1,2-dichloroethane was too small	Purify the product by additional recrystallization from hot 1,2-dichloroethane as in Step 8
12	Incomplete reaction	Reaction was stirred too slowly	Purge the reaction flask with another volume of hydrogen (~2 liters), increase the stirring and continue the hydrogenation reaction until the full substrate (and intermediate) conversion
23	Incomplete reaction	See Possible reason for Step 12	See Solution for Step 12
29	Impurities observed by additional signals observed in the $^{31}P\{^1H\}$ NMR spectrum	Presence of water in the substrate or solvents, impurities in PCl_3, wet glassware, argon line or septum and so on, and the Schlenk setup leaks allowing the air/moisture to get inside	Check the purity of PCl_3 and solvents. Dry the argon line. Repeat the synthesis with all well-predried glassware, stirring bars and so on
	Residual PCl_3 signal observed at the $^{31}P\{^1H\}$ NMR spectrum	Incomplete evaporation of PCl_3 that was clogged in the solids	Evaporate all volatiles under vacuum using the argon-vacuum dual manifold. Add 10 ml of dry toluene and again evaporate the volatiles
33	Impurities observed by additional signals observed at the $^{31}P\{^1H\}$ NMR spectrum	See Possible reason for Step 29; or wrong ratio between building blocks **6** and **7** because of impurities	See Solution for Step 29. Check the purity of compound **6** and (S)-binol used for synthesis of compound **7**
47	Incomplete reaction	Ligand **L1** is hydrolyzed owing to presence of water in the reaction mixture	Check the purity of reagents and solvents. Repeat the reaction with all well-predried glassware, stirring bars and so on

● TIMING

Steps 1–9, preparation of compound **3**: 1 d
Steps 10–20, preparation of compound **5**: 2 d
Steps 21–26, preparation of compound **6**: 1 d
Steps 27–29, preparation of compound **7**: 4 h
Steps 30–33, preparation of ligand **L1**: 2 d
Steps 34–41, general procedure
Steps 40–47, catalytic preparation of 2-(3-oxopropane)-benzoic acid **2a**: 20 h

ANTICIPATED RESULTS

Typical yields

The preparative yields for the whole process are variable and are somewhat dependent on the scale of the reactions. The isolated yields may vary because of losses during purification and isolation, and are in the range of 30–45% for compound **3**, 70–90% for compound **5**, 95–100% for compound **6**, 85–100% for compound **L1** and 88–98% for compound **2a**. The representative yields are provided for reactions conducted on the scale described in the protocol.

Preparation of 1,1-bis-(-3-methyl-7-nitro-1H-indol-2-yl)-propane (3)

23.7 g (44%) of an orange crystalline powder; melting point, 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (bs, 2H, NH), 8.09 (d, J = 8 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H), 7.17 (dd, J = 7.9 Hz, 2H), 4.53 (t, J = 8 Hz, 1H, C*H*CH_2), 2.35 (m, CH_2), 2.32 (s, 6H, CH_3) and 1.07 (t, J = 7.2 Hz, 3H, C$H_3$$CH_2$); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 136.6, 133.3, 132.7, 129.0, 126.5, 119.0, 109.6, 37.3, 26.5, 12.5 and 8.8; HRMS (EI): [M^{+}] calculated for $C_{21}H_{20}N_4O_4$: 392.14846; found: 392.14746.

Preparation of bis-(4-(benzyloxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane) (5)

5.40 g (81%) of a colorless/off-white powder; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24 (bs, 2H), 9.95 (bs, 2H), 7.94 (d, J = 8.7 Hz, 4H), 7.49–7.29 (m, 12H), 7.25 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 8.7 Hz, 4H), 6.96 (t, J = 7.7 Hz, 2H), 5.17 (t, J = 2.6Hz, 4H, PhCH_2), 4.50 (t, J = 8.2 Hz, 1H, C*H*CH_2CH_3), 2.24 (s, 6H, ArCH_3), 2.20 (m, 2H, CHCH_2CH_3) and 0.91 (t, J = 7.2 Hz, 3H, $CHCH_2$CH_3); ^{13}C {^{1}H} NMR (100.MHz, DMSO-d_6): δ 165.0, 160.8, 136.6, 135.7, 130.4, 129.8, 128.5, 127.9, 127.7, 127.4, 122.9, 118.3, 114.9, 114.6, 114.4, 106.4, 69.4, 35.9, 26.6, 12.2 and 8.6; HRMS (FAB): [M+H]$^{+}$ calculated for $C_{49}H_{45}N_4O_4$: 753.3441; found: 753.3447.

Preparation of bis-(4-(hydroxy)benzoamide) of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane) (6)

4.15 g (100%) of a colorless/off-white powder; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.26 (bs, 2H), 10.07 (bs, 2H), 9.84 (bs, 2H), 7.84 (d, J = 8.7 Hz, 4H), 7.35 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 6.95 (dd, J = J = 7.9 Hz, 2H), 6.85 (d, J = 8.7 Hz, 4H), 4.49 (t, J = 8.0 Hz, 1H, C*H*CH_2CH_3), 2.22 (s, 6H, ArCH_3), 2.19 (m, 2H, CHCH_2CH_3) and 0.91 (t, J = 7.2 Hz, 3H, $CHCH_2$CH_3); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6): δ 165.3, 160.5, 135.6, 130.4, 129.9, 128.3, 125.6, 123.1, 118.3, 114.9, 114.7, 114.4, 106.3, 36.0, 26.6, 12.2 and 8.6; HRMS (FAB): [M+H]$^{+}$ calculated for $C_{35}H_{33}N_4O_4$ 573.2502; found: 573.2499.

Preparation of ligand L1

2.40 g (93%) of a pale yellow powder of ligand **L1**, cyclohexane adduct. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.58 (s, 2H), 8.24 (s, 1H), 8.21 (s, 1H), 8.07–7.80 (m, 8H), 7.71–7.62 (m, 4H), 7.53–7.20 (m, 18H), 7.15–6.94 (m, 8H), 4.45 (t, J = 7.9 Hz, 1H, C*H*CH_2CH_3), 2.32 (pd, 6H, 2•ArCH_3), 2.19 (dt, J = J = 7.4 Hz, 2H, CHCH_2CH_3) and 0.92 (t, J = 7.3 Hz, 3H, $CHCH_2$CH_3); ^{13}C {^{1}H} NMR (100 MHz, CD_2Cl_2): δ 165.5 (s), 155.0 (d, J = 7.6 Hz), 147.8 (d, J = 3.9 Hz), 147.2 (s), 136.4 (d, J = 6.0 Hz), 133.0 (d, J = 32.0 Hz), 132.3 (d, J = 9.0 Hz), 131.7 (s), 131.1 (s), 130.8 (s), 130.5 (s), 129.9 (s), 128.9 (d, J = 5.5 Hz), 128.3 (d, J = 5.5 Hz), 127.2 (d, J = 15.0 Hz), 126.8 (d, J = 9.5 Hz), 125.7 (d, J = 19.1 Hz), 124.6 (d, J = 4.9 Hz), 124.4 (d, J = 17.0 Hz), 123.2 (d, J = 1.4 Hz), 122.5 (d, J = 1.4 Hz), 121.9 (d, J = 5.5 Hz), 120.5 (d, J = 2.5 Hz), 120.4 (d, J = 2.5 Hz), 119.3 (s), 116.1 (d, J = 2.0 Hz), 114.2 (d, J = 3.4 Hz), 108.1 (d, J = 7.6 Hz), 36.8 (s), 27.8 (s), 12.5 (s) and 8.9 (s); ^{31}P {^{1}H} NMR (162 MHz, CD_2Cl_2): δ 143.8. HRMS (FAB): [M+H]$^{+}$ calculated for $C_{75}H_{55}N_4O_8P_2$: 1201.3495, found: 1201.3497; elemental analysis (%) calculated for 2•$C_{75}H_{54}N_4O_8P_2$•C_6H_{12}: C 75.35, H 4.86, N 4.51, P 4.98, found: C 75.19, H 4.49, N 4.26, P 4.97.

Preparation of 2-(3-oxopropane)-benzoic acid (2a)

5.20 g (97.4%) of a white crystalline powder; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.92 (bs, 1H, COO*H*), 9.71 (t, J = 1.3 Hz, 1H, C*H*O), 7.81 (dd, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.47 (ddd, J = J = 7.6 Hz, J = 1.4 Hz, 1H), 7.36–7.28 (m, 2H) 3.16 (t, J = 7.5 Hz, 2H, C$H_2$$CH_2$CHO) and 2.74 (td, J = 7.5 Hz, J = 1.3 Hz, 2H, CH_2CHO); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6): δ = 202.6, 168.6, 142.0, 131.9, 130.9, 130.4, 130.3, 126.3, 44.8 and 26.4; HRMS (FAB): [M+H]$^{+}$ calculated for $C_{10}H_{11}O_3$: 179.0708, found: 179.0707; elemental analysis (%) calculated for $C_{10}H_{10}O_3$: C 67.41, H 5.66; found: C 67.41, H 5.65.

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