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Efficient Stereoselective Synthesis of a Key Chiral Aldehyde Intermediate in the Synthesis of Picolinamide Fungicides

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Supporting Information

ABSTRACT: A highly stereoselective and efficient synthesis of (4*S*,5*S*,6*S*)-6-(benzyloxy)-5-phenoxy-4-propoxyheptanal, a key intermediate for syntheses of picolinamide fungicides, is described in this report. The synthesis features a scalable allylpropyl ether preparation, an efficient synthesis of the C1−C3 *anti,syn*-(*S*,*S*,*S*) stereotriad via a highly diastereoselective allylboration, and Cu-catalyzed phenylation of a sterically hindered secondary alcohol with $BiPh_3(OAc)_2$ followed by highly regioselective hydroformylation with the formation of a linear aldehyde. Excellent overall route efficiency was achieved (six steps and 39% yield) starting from readily available and inexpensive (*S*)-ethyl lactate.

KEYWORDS: *stereoselective allylboration, allyl propyl ether preparation, B-(Z)-γ-(propoxyallyl)diisopinocampheylborane, phenylation, organobismuth, hydroformylation, picolinamide fungicides*

INTRODUCTION

Fungicides are key agricultural inputs for the control of plant diseases that can dramatically reduce the yield of crops.[1] Several factors necessitate the development of fungicides with new modes of action. Because of their rapid rate of reproduction, plant pathogens can develop resistance to fungicides that limit their utility over time. In addition, many fungicides have been removed from use by regulatory agencies because of safety concerns.[2] Our efforts to identify new crop protection products to meet these needs led to the discovery of a novel class of cyclic and acyclic picolinamide fungicides (Figure 1).[3] During these efforts, (4*S*,5*S*,6*S*)-6-(benzyloxy)-5-phenoxy-4-propoxyheptanal (**1**) was proposed as a key synthetic intermediate. We envisioned that intermediate **1** would enable retrosynthetic approaches to picolinamide fungicides in which the aldehyde functionality could participate in Wittig, Horner−Wadsworth−Emmons, Knoevenagel, and aldol chemistry. Compound **1** has several structural features that posed synthetic challenges. The presence of three contiguous stererocenters (C4, C5, and C6) with *S*,*S*,*S* absolute configuration required efficient control of both the relative and absolute stereochemistry. In addition, the presence of two different ether moieties at C4 and C5 required these alcohols to be differentiated. Finally, the presence of a terminal aldehyde in **1** required a strategy to install this reactive functional group at a late stage. In this report, we describe an efficient and stereoselective route to compound **1**.

RESULTS AND DISCUSSION

Retrosynthetically, we envisioned that compound **1** could be obtained by hydroformylation of olefin **2**, which would result from late-stage phenylation of alcohol **3** (Scheme 1). Through methodology developed by Brown,[4] allylboration of known aldehyde **6**[5] with (*Z*)-di-^{l}Ipc-allylborane **5** (Ipc = isopinocampheyl) was proposed to generate the C2−C4 *anti,syn*-(*S*,*S*,*S*) stereotriad of compound **3**, presumably via cyclic chairlike transition state **4**.[6] We anticipated high stereoselectivity toward the desired *S*,*S* C3 and C4 chiral centers due to the matched double asymmetric induction of (*S*)-lactate-derived aldehyde **6** with borane **5** derived from allyl *n*-propyl ether (**7**).

Known aldehyde **6** was prepared on a 0.5 kg scale from (*S*)-ethyl lactate (**8**) using a modified literature procedure (Scheme 2).[5a] Reaction of **8** with pyrrolidine in the absence of solvent afforded amide **9** in high yield with excellent purity. Alkylation of amide **9** with benzyl chloride under phase-transfer conditions (Aliquat 336[5b] and NaOH in toluene) furnished *O*-benzyl-protected amide **10** in 88% yield. Finally, Red-Al reduction of ester **10** proceeded smoothly under mild reaction conditions without overreduction, giving rise to aldehyde **6**, which was stored under N_2 at −5 °C over several weeks without notable decomposition and erosion of enantiopurity. In contrast, although direct benzyl protection of **8** and subsequent DIBAL-H reduction afforded aldehyde **6** on a small scale, alkylation of **8** was irreproducible, and an erosion of enantiopurity was observed on scale. Furthermore, the subsequent reduction of the benzyl ester with DIBAL-H required cryogenic temperatures and was often accompanied by overreduction.

Since allyl *n*-propyl ether **7** had not been commercially available on a large scale, we developed an efficient synthesis of this raw material (Scheme 3). Because of the similar boiling points of **7** and common organic solvents, we focused on developing solvent-free conditions to avoid the need for isolation by distillation. After several conditions were screened,

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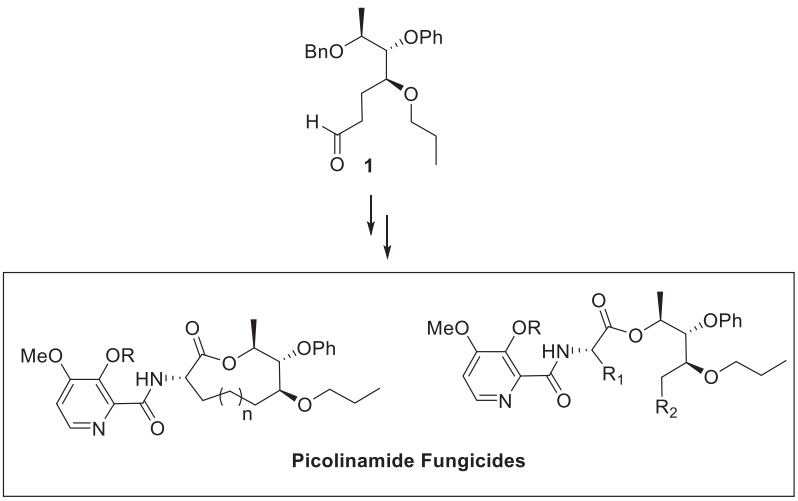
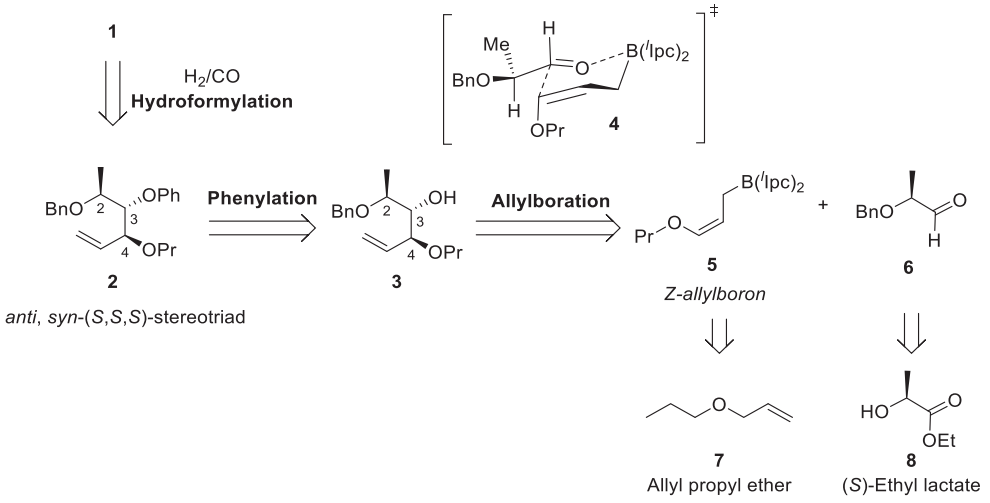
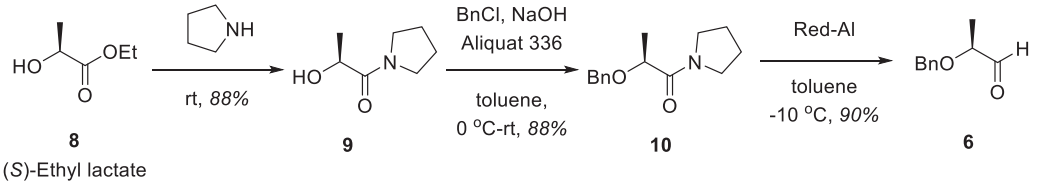


Figure 1. Compound **1** and structures of cyclic and acyclic picolinamide fungicides.

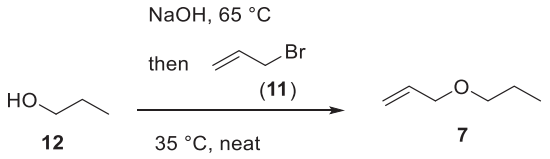
Scheme 1. Retrosynthetic Analysis toward the Synthesis of 1



Scheme 2. Large-Scale Synthesis of Aldehyde 6



Scheme 3. Synthesis of Allyl *n*-Propyl Ether (7)



the neat reaction of allyl bromide (**11**) with *n*-propanol (**12**) (1.5 equiv) was performed at 35 °C using 1.7 equiv of solid NaOH as the base. Upon completion of the reaction, excess *n*-propanol and salts were removed by successive water washes to give **7** as a neat liquid. This simple workup procedure afforded **7** with less than 3 mol % residual *n*-propanol, eliminating the need for distillation. This procedure was successfully performed on a 2.21 mol scale to yield 222 g of **7**.

With the successful scale-up of both starting materials **6** and **7**, we investigated the stereoselective formation of the C2−C4 *anti,syn*-(*S,S,S*) stereotriad in compound **3**. As shown in the allylation transition state **4** (Scheme 1), the stereoselective formation of the desired C3,C4-*syn* relative stereochemical configuration requires selective generation of (*Z*)-allylborane, which was achieved by lithiation of allyl alkyl ethers followed by transmetalation with an alkyl borate.[4] Furthermore, in a total synthesis of oleandrose, Wuts reported stereoselective formation of the 3-methoxy analogue of **3** in 84% yield as an 80:11:9 mixture of diastereomers from the reaction of aldehyde **6** with the (*Z*)-2,3-butanediolboronate of 3-

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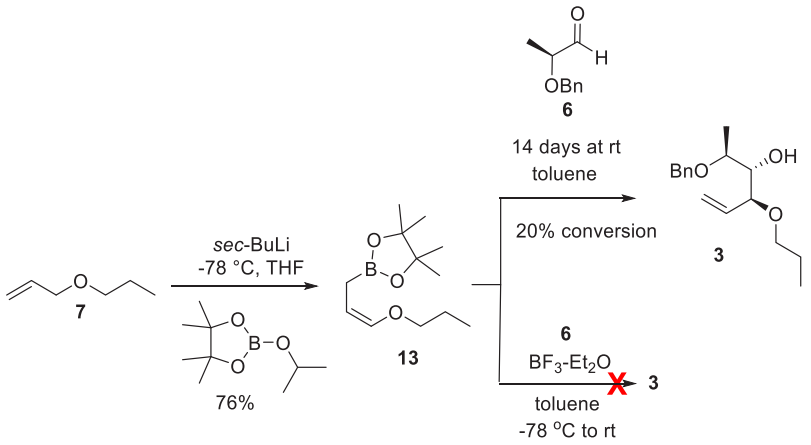
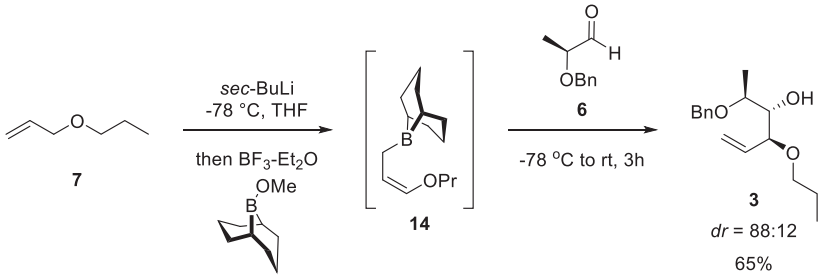
Scheme 4. Attempted Allylboration of Aldehyde 6 with Allylpinacolboronate 13



Scheme 5. Allylboration of Aldehyde 6 with 9-BBN-allylborane 14

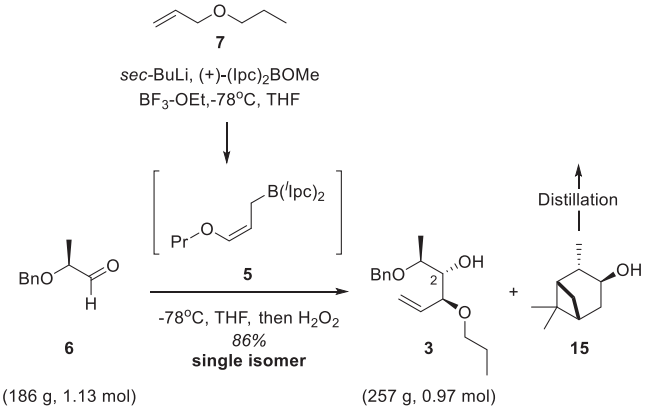


methoxypropene.[7] The major diastereomer, resulting from Felkin−Anh control, was confirmed to have *S*,*S*,*S* absolute stereochemistry by NMR characterization of its cyclohexane acetal derivative. Although these conditions led to reasonable stereoselectivity, the reaction required 7 days for completion. Not surprisingly, we found (*Z*)-allylpinacolboronate **13**, derived from **7**, to be less reactive under allylboration conditions. In this case, after 14 days at ambient temperature, the desired product **3** was formed in 15% isolated yield with less than 20% conversion of aldehyde **6** as determined by ^{1}H NMR analysis. Attempts to accelerate the reaction with a Lewis acid (BF_3·OEt_2) or at elevated temperature led to a complex reaction mixture as a result of decomposition of aldehyde **6** (Scheme 4).

Since dialkylallylboranes are typically much more reactive than their allylboronate analogues, we prepared (*Z*)-9-BBN-allylborane **14** in situ and subsequently added aldehyde **6** at −78 °C (Scheme 5). Upon warming to ambient temperature over 3 h, the desired (*S*,*S*,*S*)-alcohol **3** was isolated in 65% yield as an 88:12 mixture of two isomers as determined by ^{1}H NMR analysis.

To further improve the diastereoselectivity while maintaining an acceptable reaction time for scale-up, di-^{l}Ipc-allylborane **5** was selected for the allylboration of **3**. We envisioned that a double asymmetric induction by the matched stereochemical configurations of chiral aldehyde **3** and allylborane **5**[4] would provide improved diastereoselectivity for allylboration compared with 9-BBN-allylborane **14**. Deprotonation of allyl *n*-propyl ether **7** (119 g, 1.19 mol) with *sec*-butyllithium in cyclohexane (1.4 M, 809 mL, 1.13 mol) at −78 °C followed by sequential addition of (+)-MeOB(Ipc)$_2$ (358 g, 1.13 mol) and BF_3·OEt_2 (144 mL, 1.13 mol) generated **5**, which was directly treated with aldehyde **6** (186 g, 1.13 mol). Upon completion of the reaction, oxidative workup of the reaction mixture with H_2O_2/NaOH cleaved the borinic ester adducts to give a mixture of alcohol **3** and isopinocampheol, which was removed by Kugelrohr distillation. Neat alcohol **3** (257 g, 0.97 mol, 86%; Scheme 6) was obtained from the distillation pot with

Scheme 6. Scale-Up of the Allylboration of Aldehyde 6 with Allylborane 5



≥95% purity as determined by ^{1}H NMR analysis without further purification. ^{1}H NMR analysis of the crude product showed a single diastereomer of **3**. This procedure was successfully scaled up to provide multiple 300 g batches. Mosher ester analysis[8] of alcohol **3** confirmed the *S* absolute configuration of the C3 chiral center, and only a single isomer was observed on the basis of ^{1}H and ^{19}F NMR analyses of both (*R*)- and (*S*)-MTPA esters of **3**, which indicated complete

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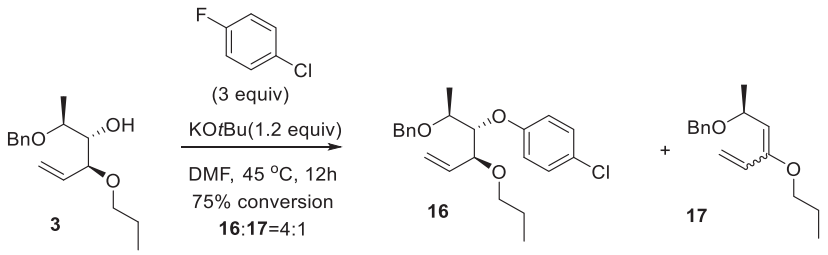
Scheme 7. S_NAr Reaction of Alcohol 3 with 4-Fluorochlorobenzene

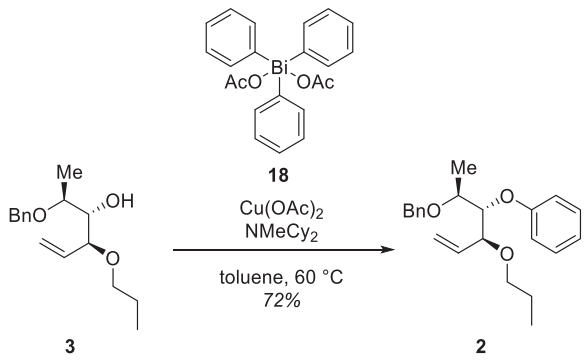


diastereoselective control of the allylboration reaction (as shown in the Supporting Information).

Next, conditions for phenylation of secondary alcohol **3** were explored. We first investigated Batey's etherification conditions ($PhBF_3K/Cu(OAc)_2/DMAP/O_2$).[9] Cu- and Pd-catalyzed cross-coupling conditions reported by Buchwald were also attempted.[10] Unfortunately, no desired product **2** was observed under either of these conditions, presumably because of the hindered nature of alcohol **3**. Subsequently, we explored the S_NAr reaction of **3** with electron-deficient 4-fluorochlorobenzene with the assumption that the activating *p*-Cl group could be removed by hydrogenation at a later stage. However, arylation of **3** with 4-fluorochlorobenzene in the presence of KO*t*Bu in DMF at 45 °C led to an inseparable 4:1 mixture of arylation product **16** and elimination product **17** with 75% conversion. Attempts to optimize this reaction did not significantly improve the **16**:**17** product ratio (Scheme 7).

After further investigation, we successfully utilized copper(II)-catalyzed phenylation of alcohol **3** with the pentavalent organobismuth reagent $BiPh_3(OAc)_2$ (**18**) for the synthesis of **2** (Scheme 8). These conditions were previously reported to

Scheme 8. Phenylation of Alcohol 3 with $BiPh_3(OAc)_2$ (18)



be effective for arylation of highly functionalized 1,2-diols.[11,12] $BiPh_3(OAc)_2$ was prepared as a white solid through the reaction of $BiPh_3$ with AcOOH (32 wt % in acetic acid) in 7:3 CH_2Cl_2/THF.[13] Phenylation of **3** was performed in toluene at 55 °C with 1.3 equiv of $BiPh_3(OAc)_2$ in the presence of 5% mol $Cu(OAc)_2$ and 1.2 equiv of dicyclohexylmethylamine (NCy_2Me) as the base. The phenylation was complete in 4 h and provided the desired compound **2** in 72% yield after column chromatography. Notably, elimination byproduct **17** was not detected under the optimized conditions.

With terminal olefin **2** in hand, Rh-catalyzed hydroformylation was explored next. We found several ligands reported in the literature that exhibited high regio- and chemoselectivity for linear hydroformylation of terminal alkenes.[14] We selected Xantphos[15] and bisphosphite **L1**[16] as ligands to study the hydroformylation of **2** (Scheme 9). Hydroformylation of olefin **2** with the catalyst prepared in situ from 1 mol % $Rh(CO)_2(acac)$ and 1 mol % Xantphos in THF at 75 °C under 1000 psi 1:1 H_2/CO gave the linear aldehyde **2** in 61% isolated yield after column chromatography. Observation of a triplet at δ 9.68 (J = 1.6 Hz) in the ^1H NMR spectrum of **2** confirmed the product to be the linear aldehyde regioisomer. The branched isomer was not observed in the ^1H NMR spectrum of the crude product mixture. The high regioselectivity is presumably due to the significant steric difference between the terminal C6 and internal C5 of the olefin.

Hydroformylation of **2** using 0.1 mol % $Rh(CO)_2(acac)$ and 0.2 mol % bisphosphite **L1** at 70 °C under 100 psi 1:1 H_2/CO gave aldehyde **1** in 90% isolated yield. Bisphosphite **L1** provided several significant advantages over Xantphos. Use of **L1** allowed the hydroformylation reaction to be performed at lower CO pressure, reaction temperature, and Rh loading than with Xantphos as the ligand. More importantly, the polarity of the aldehyde product combined with the nonpolar nature of the Rh−**L1** catalyst system facilitated product isolation and catalyst recovery by nonaqueous biphasic extraction with subsequent catalyst recycling.[17,18] Following hydroformylation of **2** with Rh−**L1** in heptane at 70 °C in the next experiment, acetonitrile was added, and aldehyde **1** was isolated in 84% yield (97.2% purity by gas chromatography) by evaporation of the acetonitrile layer. A small amount of hydrogenation side-product **20** (1 area % by GC) was observed in the sample. The heptane layer contained a small amount of the aldehyde product (5% yield) along with byproduct **20** in a 91:9 ratio. The combined product yield was 91%. The catalyst was mostly partitioned into the heptane layer and was recycled for an additional hydroformylation experiment, which gave **1** in 64% yield with 95% purity after isolation.

CONCLUSIONS

A scalable and highly stereoselective route to (4*S*,5*S*,6*S*)-6-(benzyloxy)-5-phenoxy-4-propoxyheptanal (**1**), an advanced intermediate for picolinamide fungicides, was developed. The key route designs included a matched double asymmetric allylboration of aldehyde **6** with (*Z*)-di-^{l}Ipc-allylborane **5** to provide compound **3** containing the synthetically challenging C2−C4 *anti*,*syn*-stereotriad as a single isomer. A mild Cu-catalyzed arylation of sterically hindered secondary alcohol **3** with $BiPh_3(OAc)_2$ and a hydroformylation process to form the terminal aldehyde with excellent regio- and chemoselectivity were demonstrated. A practical preparation of allyl *n*-propyl ether (**7**) was also developed. The overall route efficiency for **1** is excellent (six steps and 39% overall yield) starting from (*S*)-ethyl lactate. With the exception of the phenylation step, all of

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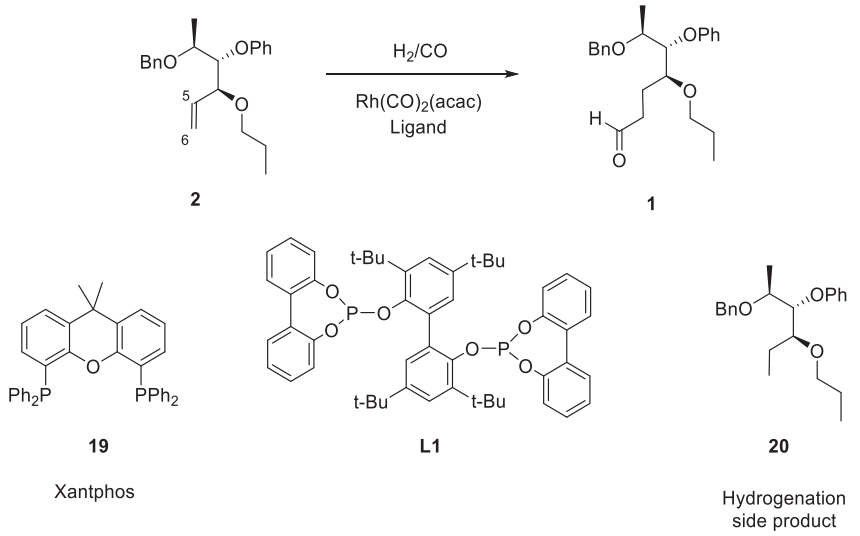
Scheme 9. Preparation of Aldehyde 1 by Rh-Catalyzed Hydroformylation of 2 with Xantphos and L1



the column chromatographic purifications were avoided by implementing scalable distillation, extraction, and recrystallization processes. Moreover, the combination of the Brown allylboration with Rh-catalyzed regioselective hydroformylation to a linear aldehyde is a powerful strategy for the synthesis of complex aliphatic aldehydes with multiple contiguous stereocenters, as illustrated by a recent example of the cascade asymmetric synthesis of tetrahydropyran derivatives.[19] We have utilized this strategy extensively for the preparation of aldehyde intermediates analogous to **1**, which were further derivatized to successfully support our internal discovery field sample synthesis and structure−activity relationship studies. We believe that the asymmetric allylboration−hydroformylation reaction sequence is an effective methodology for asymmetric synthesis of structurally complex aldehydes.

EXPERIMENTAL SECTION

General. All of the reagents were commercially available and used as purchased without further purification. Unless otherwise noted, all of the reactions were performed in round-bottom or jacketed cylindrical flasks under nitrogen. ^{1}H NMR spectra were recorded on a Bruker Ultrashield 400 NMR spectrometer or a Varian 400-MR spectrometer. Mass spectra were obtained using a Waters Micromass ZQ mass spectrometer. HPLC analysis was performed using an Agilent 1260 chromatograph with a YMC Pack-ODS-AQ column (4.6 mm × 150 mm, 5.0 μm, P/N 0415212347); GC analyses were performed using an Agilent 7890 chromatograph with samples prepared by weighing approximately 0.05 g of the material into a 2 mL glass GC vial and diluting with about 1.5 mL of acetone. GC results are expressed in area %. GC/MS analyses were performed on an HP 7890A series GC system with an RVM Scientific low thermal mass (LTM) 15 m × 250 μM × 0.25 μM Varian VF-5MS column using a 5795 EI/CI mass-selective detector in chemical ionization (CI) positive ion mode.

(*S*)-2-Hydroxy-1-(pyrrolidin-1-yl)propan-1-one (9). A 2 L round-bottom flask equipped with a thermocouple and nitrogen inlet was charged with (*S*)-ethyl lactate (**8**) (0.485 L, 4.15 mol). The flask was cooled to −1 °C, and pyrrolidine (0.520 L, 6.22 mol) was added via addition funnel over 1 h at such a rate that the internal temperature was kept below 5 °C. The reaction mixture was allowed to warm gradually to room temperature (rt) over 72 h. The reaction mixture was concentrated under vacuum (1 Torr, 50 °C) to afford (*S*)-2-hydroxy-1-(pyrrolidin-1-yl)propan-1-one (**9**) (550 g, 3.84 mol, 97% purity by ^{1}H NMR, 90% yield). The spectroscopic data for **9** were consistent with values reported in the literature.[5] $[\alpha]_D^{20}$ −48.7 (*c* 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 1H), 3.60−3.44 (m, 1H), 3.44−3.34 (m, 2H), 3.27 (m, *J* = 10.2, 7.0 Hz, 1H), 2.01−1.87 (m, 2H), 1.87−1.74 (m, 2H), 1.26 (d, *J* = 6.6 Hz, 3H).

(*S*)-2-(Benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one (10). A 5 L three-neck round-bottom flask equipped with overhead stirring, a temperature probe, an addition funnel, and a N_2 inlet was charged with benzyl chloride (282 mL, 2.42 mol), *N*-methyl-*N*,*N*,*N*-trioctylammonium chloride (37.6 g, 93 mmol), and toluene (2.1 L). The flask was cooled to 0 °C, and powdered NaOH (269 g, 6.52 mol) was added. Compound **9** (275 g, 97% purity, 1.86 mol) was added over 40 min via addition funnel while the internal temperature was maintained at <10 °C. After complete addition, the reaction mixture was warmed to rt, stirred for 4 h, and then poured into rapidly stirring cold 2 M HCl. The phases were partitioned, and the organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Hexanes (1 L) was added, and the biphasic mixture (hexanes/crude oil) was stirred at −78 °C to initiate crystallization. Crystalline (*S*)-2-(benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one (**10**) (272 g) was collected via filtration. The filtrate was purified via flash column chromatography over silica gel to afford additional **10** (88 g, 360 g combined, 1.54 mol, 98% purity, 81% yield). The spectroscopic data for **10** were consistent with values reported in the literature.[5] $[\alpha]_D^{20}$ −61.5 (*c* 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.16 (m, 5H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.12 (q, *J* = 6.7 Hz, 1H), 3.50−3.38 (m, 2H), 3.38−3.29 (m, 2H), 1.88−1.78 (m, 2H), 1.78−1.69 (m, 2H), 1.34 (d, *J* = 6.7 Hz, 3H).

(*S*)-2-(Benzyloxy)propanal (6). A 5 L three-neck round-bottom flask equipped with overhead stirring, a thermocouple, an addition funnel, and a N_2 inlet was charged with **10** (500 g, 2.1 mol) and anhydrous toluene (2.3 L). The flask was cooled to −12 °C, and a 60 wt % solution of Red-Al in toluene was added over 30 min via addition funnel. The reaction mixture

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was stirred between −13 and −10 °C for 2.5 h, and the reaction was quenched with acetone (100 mL). The mixture was stirred for 10 min and then poured into HCl (6.5 L, 1 N) at 0 °C. The phases were partitioned, and the aqueous layer was back-extracted with ethyl acetate (2.5 L). The combined organic extracts were washed with dilute HCl (0.1 M), dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-2-(benzyloxy)propanal (**6**) (326 g, 1.98 mol, 95% purity, 90% yield) as an oil. The spectroscopic data for **6** were consistent with values reported in the literature.[5] $[\alpha]_D^{20}$ −58.44 (neat). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, J = 1.8 Hz, 1H), 7.45−7.28 (m, 5H), 4.94−4.44 (m, 2H), 3.90 (qd, J = 6.9, 1.8 Hz, 1H), 1.34 (d, J = 6.9 Hz, 3H).

3-Propoxyprop-1-ene (7). A 1 L three-neck round-bottom flask equipped with overhead stirring, a nitrogen inlet, a thermocouple, and an addition funnel was charged with 1-propanol (297 mL, 3.97 mol). NaOH (pellets, 180 g, 4.50 mol) was added in one portion, and the internal temperature rose to 40 °C. The mixture was then heated to 65 °C and stirred for 20 min. The suspension was cooled to 35 °C, and allyl bromide (229 mL, 2.65 mol) was added over 1 h via addition funnel while the internal temperature was maintained between 35 and 55 °C. After complete addition, the reaction mixture was stirred for 20 h and then cooled to 0 °C, and water (500 mL) was added. The biphasic mixture was stirred for 10 min, after which the layers were partitioned and the organic layer was washed with water (2 × 500 mL) and brine (2 × 500 mL) to afford 3-propoxyprop-1-ene (**7**) (222 g, 2.21 mol, 84%) as a yellow oil with ≤3 mol % propanol by ^{1}H NMR analysis. *Note:* **7** could be further purified by distillation (bp = 91 °C, 760 Torr) if desired. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99−5.80 (m, 1H), 5.25 (dq, J = 17.2, 1.7 Hz, 1H), 5.18−5.11 (m, 1H), 4.07−3.80 (m, 2H), 3.37 (t, J = 6.7 Hz, 2H), 1.70−1.45 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.18, 116.62, 72.14, 71.81, 23.02, 10.62.

(2*S*,3*S*,4*S*)-2-(Benzyloxy)-4-propoxyhex-5-en-3-ol (3). A 5 L three-neck round-bottom flasked equipped with overhead stirring, a nitrogen inlet, a thermocouple, and an addition funnel was charged with **7** (119 g, 1.19 mol) and anhydrous THF (900 mL). The flask was cooled to −78 °C, and a solution of *sec*-butyllithium in cyclohexane (1.4 M, 809 mL, 1.13 mol) was added in three portions over 1.5 h via addition funnel while the internal temperature was maintained below −65 °C. The mixture was stirred for 1 h, and then a solution of (+)-MeOB(Ipc)$_2$ (358 g, 1.13 mol) in anhydrous THF (200 mL) was added over 1.5 h via addition funnel while the internal temperature was maintained below −65 °C. The resultant mixture was stirred for 1.5 h, and then $BF_3{\cdot}Et_2O$ (144 mL, 1.13 mol) was added via addition funnel as quickly as possible while the internal temperature was maintained below −65 °C. Aldehyde **6** (186 g, 1.13 mol) was added over 1 h via addition funnel while the internal temperature was maintained below −65 °C. The reaction mixture was allowed to warm gradually overnight for 16 h. The flask was cooled to 8 °C, and NaOH (6 M, 226 mL, 1.36 mol) was added. Then 30% aqueous H_2O_2 (454 mL) was added in two portions over 2 h via addition funnel while the internal temperature was maintained below 30 °C. The mixture was stirred for 1 h, after which the layers were partitioned and the aqueous layer was back-extracted with MTBE (3 × 300 mL). The combined extracts were washed with saturated $NaHSO_3$ (800 mL) and brine (800 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting crude oil was subjected to Kugelrhor distillation (65−70 °C, 0.4−0.6 Torr) to remove isopinocampheol, affording (2*S*,3*S*,4*S*)-2-(benzyloxy)-4-propoxyhex-5-en-3-ol (**3**) (257 g, 0.97 mol, 86%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.33 (m, 4H), 7.32−7.26 (m, 1H), 5.76 (ddd, J = 17.2, 10.4, 7.5 Hz, 1H), 5.28 (ddd, J = 8.9, 1.8, 0.9 Hz, 1H), 5.28−5.22 (m, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 3.83 (ddt, J = 7.5, 4.5, 0.9 Hz, 1H), 3.58 (p, J = 6.1 Hz, 1H) 3.53−3.43 (m, 2H), 3.18 (dt, J = 9.61, 6.6 Hz, 1H), 2.42 (d, J = 5.8 Hz, 1H), 1.62−1.45 (m, 2H), 1.27 (d, J = 6.2 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 135.9, 128.3, 127.8, 127.5, 118.3, 80.2, 76.2, 74.7, 70.7, 70.5, 23.0, 15.3, 10.7. HRMS-ESI (m/z): calcd for $C_{16}H_{25}O_3$ ($[M + H]^+$), 265.1798; found, 265.1793.

(((2*S*,3*S*,4*S*)-2-(Benzyloxy)-4-propoxyhex-5-en-3-yl)-oxy)benzene (2). A 3 L four-neck round-bottom flask was charged with **3** (93 g, 0.35 mol), toluene (1.17 L), $BiPh_3(OAc)_2$ (269 g, 0.46 mol), $Cu(OAc)_2$ (3.29 g, 17.6 mmol), and *N*,*N*-dicyclohexylmethylamine (91 mL, 0.42 mol). The reaction mixture was heated to 55 °C and stirred for 4 h. *Note:* the reaction was exothermic and became self-heating, and the internal temperature was maintained between 55 and 60 °C. The reaction mixture was cooled to rt and filtered through a pad of Celite. The filtrate was partitioned between EtOAc (1 L) and 1 M HCl (0.50 L). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (0.50 L). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified via flash column chromatography over silica gel (0−10% EtOAc/hexanes) to afford (((2*S*,3*S*,4*S*)-2-(benzyloxy)-4-propoxyhex-5-en-3-yl)oxy)benzene (**2**) (91 g, 0.27 mol, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.17 (m, 7H), 7.11−6.99 (m, 2H), 6.96−6.85 (m, 1H), 5.81 (ddd, J = 17.3, 10.3, 7.9 Hz, 1H), 5.31 (ddd, J = 17.3, 1.9, 1.0 Hz, 1H), 5.22 (ddd, J = 10.3, 1.8, 0.8 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 4.30 (dd, J = 6.4, 4.0 Hz, 1H), 4.07 (ddt, J = 7.8, 3.9, 0.9 Hz, 1H), 3.97 (p, J = 6.3 Hz, 1H), 3.51 (dt, J = 9.3, 6.7 Hz, 1H), 3.23 (dt, J = 9.3, 6.8 Hz, 1H), 1.59 (h, J = 7.2 Hz, 2H), 1.26 (d, J = 6.3 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.13, 138.70, 136.32, 129.40, 128.50, 127.87, 127.69, 121.10, 118.42, 116.76, 83.67, 80.90, 74.42, 71.13, 71.11, 23.13, 16.19, 10.89. HRMS-ESI (m/z): calcd for $C_{22}H_{29}O_3$ ($[M + H]^+$), 340.2038; found, 340.2022.

Synthesis of (4*S*,5*S*,6*S*)-6-(Benzyloxy)-5-phenoxy-4-propoxyheptanal (1) Using Rh−Xantphos (1 mol % Rh). Compound **2** (1.95 g, 5.73 mmol) was placed in a 40 mL Parr reactor. THF (5 mL) was added. $Rh(CO)_2(acac)$ (15 mg, 1 mol %) and Xantphos (33 mg, 1 mol %) were added as solids. The reactor was purged three times with CO, pressurized to 1000 psi 1:1 H_2/CO, and heated to 75 °C for 18 h. After cooling, the reactor was vented, and the contents were rotary-evaporated to obtain a very dark oil. The crude product was loaded onto a 5 g silica cartridge using CH_2Cl_2. Flash chromatography on a 40 g Isco Gold column (hexane/EtOAc gradient) gave 1.30 g of **1** as a colorless liquid (61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (t, J = 1.6 Hz, 1H), 7.38−7.18 (m, 7H), 7.03 (dt, J = 7.9, 1.1 Hz, 2H), 6.97−6.88 (m, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.35 (t, J = 5.0 Hz, 1H), 3.89 (qd, J = 6.3, 5.1 Hz, 1H), 3.59 (dt, J = 8.3, 4.6 Hz, 1H), 3.45 (ddt, J = 39.1, 8.9, 6.8 Hz, 2H), 2.47 (td, J = 7.2, 1.6 Hz, 2H), 2.01−1.78 (m, 2H), 1.59−1.42 (m, 2H), 1.29 (d, J = 6.3 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.98, 159.57, 138.40,

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129.42, 128.37, 127.63, 127.58, 121.02, 116.15, 82.25, 78.55, 74.58, 73.22, 70.68, 40.20, 23.94, 23.31, 15.87, 10.62. HRMS-ESI (m/z): calcd for $[C_{23}H_{30}O_4]^+$, 370.2144; found, 370.2145.

Synthesis of 1 Using Rh−L1 (0.2 mol % Rh, L1/Rh = 2) at 60 °C and 100 psi Syngas. $Rh(CO)_2acac$ (12.9 mg; 0.05 mmol) and **L1** (83.9 mg; 0.1 mmol) were dissolved in nitrogen-purged heptane (20 mL) with stirring. A portion of this solution (10 mL; 0.025 mmol Rh and 0.05 mmol L) was charged to a syngas-purged Parr reactor by syringe. Then syngas was charged to the reactor at 60 psi, and the solution was heated at 70 °C for 30 min with the pressure adjusted to 100 psi. The mixture was cooled to 30 °C, and the syngas was vented, after which **2** (4.26 g, 12.5 mmol, 96.7% pure by GC) in heptane (4 mL) was quickly charged via syringe. The reactor was heated to 60 °C at 100 psi with stirring. After 2 h, GC analysis revealed reaction completion. The reactor contents were cooled and diluted to a total volume of 170 mL with heptane. This solution was mixed with an equal volume of acetonitrile and shaken in a separatory funnel. The phases were separated and analyzed. The acetonitrile phase contained about 97.2 GC area % aldehyde **1** and about 1.0 GC area % hydrogenated olefin (reaction side product), while the heptane phase showed 81.8 GC area % aldehyde **1** and 8.8 GC area % hydrogenated olefin. Solvent evaporation produced 3.87 g of aldehyde **1** from the acetonitrile phase and 0.325 g of the remaining product from the heptane phase (total 4.20 g, 11.30 mmol, 91% yield).

Catalyst Recycling Using Rh−L1 (0.5 mol % Rh, L1/Rh = 2) at 60 °C and 100 psi Syngas. The reaction described above was repeated using 0.85 g (2.50 mmol) of olefin **2** in 12 mL of heptane, and upon reaction completion the reaction mixture was extracted with an equal by volume amount of acetonitrile. After phase separation, the solvent was evaporated from the acetonitrile phase to give 0.72 g (78% yield) of the aldehyde product **1** with 97.6% GC purity. The heptane phase, which mostly contained the catalyst/ligand, was reused in the next cycle of hydroformylation with the same amount of the starting olefin **2**. Upon reaction completion, the mixture was treated with an equal by volume amount of acetonitrile, the phases were separated, and the solvent was evaporated from the acetonitrile phase to give 0.59 g (64% yield) of the aldehyde product **1** with 95.1% GC purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00310.

Mosher ester analysis of **3** and ^1H and ^{13}C NMR spectra of compounds **3**, **2**, and **1** (PDF)

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The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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