JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

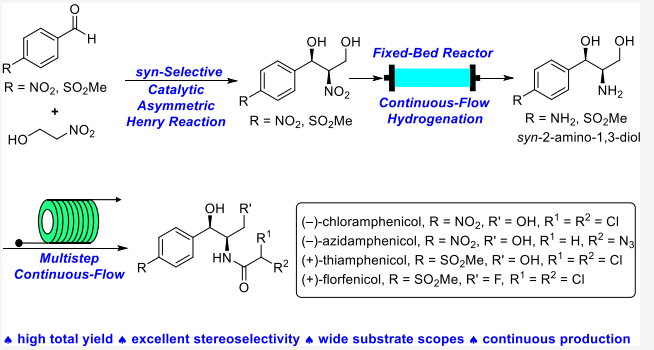
Catalytic *Syn*-Selective Nitroaldol Approach to Amphenicol Antibiotics: Evolution of a Unified Asymmetric Synthesis of (−)-Chloramphenicol, (−)-Azidamphenicol, (+)-Thiamphenicol, and (+)-Florfenicol

Yingqi Xia, Meifen Jiang, Minjie Liu, Yan Zhang, Hongmin Qu, Tong Xiong, Huashan Huang, Dang Cheng, and Fener Chen*

Cite This: https://doi.org/10.1021/acs.joc.1c01124 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A unified strategy for an efficient and high diastereo- and enantioselective synthesis of (−)-chloramphenicol, (−)-azidamphenicol, (+)-thiamphenicol, and (+)-florfenicol based on a key catalytic *syn*-selective Henry reaction is reported. The stereochemistry of the ligand-enabled copper(II)-catalyzed aryl aldehyde Henry reaction of nitroethanol was first explored to forge a challenging *syn*-2-amino-1,3-diol structure unit with vicinal stereocenters with excellent stereocontrol. Multistep continuous flow manipulations were carried out to achieve the efficient asymmetric synthesis of this family of amphenicol antibiotics.



INTRODUCTION

Amphenicols are a class of important synthetic antibiotics, which exhibit a broad spectrum of activity against both Gram-negative and Gram-positive microorganisms, such as *Streptococcus* spp., *Staphylococcus* spp., *Pasteurella* spp. etc.[1] (−)-Chloramphenicol (**1**), (−)-azidamphenicol (**2**), (+)-thiamphenicol (**3**), and (+)-florfenicol (**4**) (Figure 1) are typical members of this family of antibiotics. They have been used effectively for the treatment of susceptible and serious bacterial infections in both human and livestock.[2] Due to the lack of treatment options for multidrug-resistant (MDR) bacterial infections with a global spread in the last few decades, which stand for a serious public health emergency, currently, this class of amphenicol antibiotics has been reintroduced as antibacterial therapy for some infectious diseases,[3] despite their undesirable side effects to patients. Once further evidence supports the broad clinical use of these older antibiotics for the bacterial infections caused by MDR microorganisms, the bulk supply of the active pharmaceutical ingredients for cost-effective and highly stereocontrolled manufacture of these amphenicol antibiotics would be an urgent concern.[4] Structurally, these amphenicol antibiotics (**1**−**4**) share a common chiral *syn*-2-amino-1,3-diol subunit, harboring two adjacent stereocenters, which presents a huge challenge to large-scale synthesis. Thus, this came as a driving force for the development of a variety of strategies for the construction of this highly functionalized *syn*-2-amino-1,3-diol moiety bearing (1*R*,2*R*)-vicinal stereocenters existing in this family of amphenicol antibiotics. To date, a number of asymmetric synthetic approaches toward the targeted amphenicol molecules have been reported.[5] Typical methods include Corey's chiral diazaborolidine-mediated asymmetric aldol reaction,[5a] Hajra's

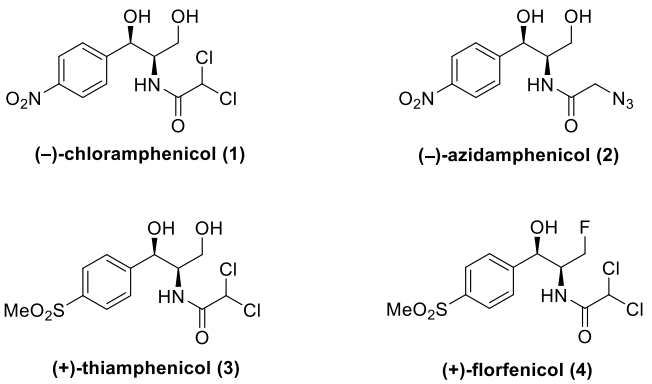
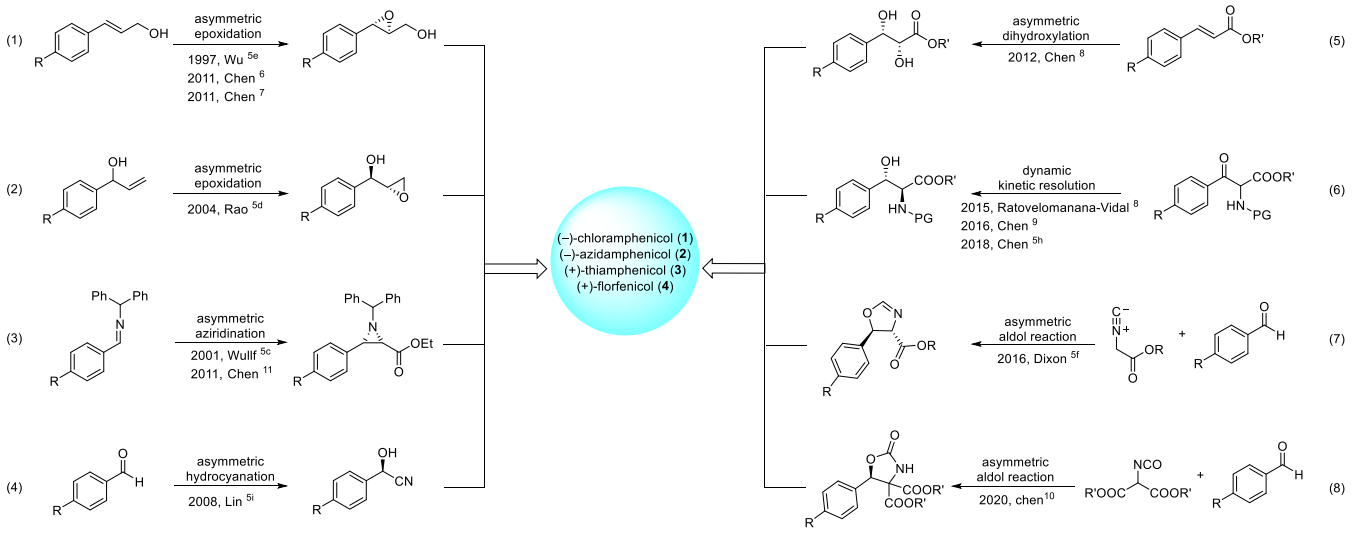


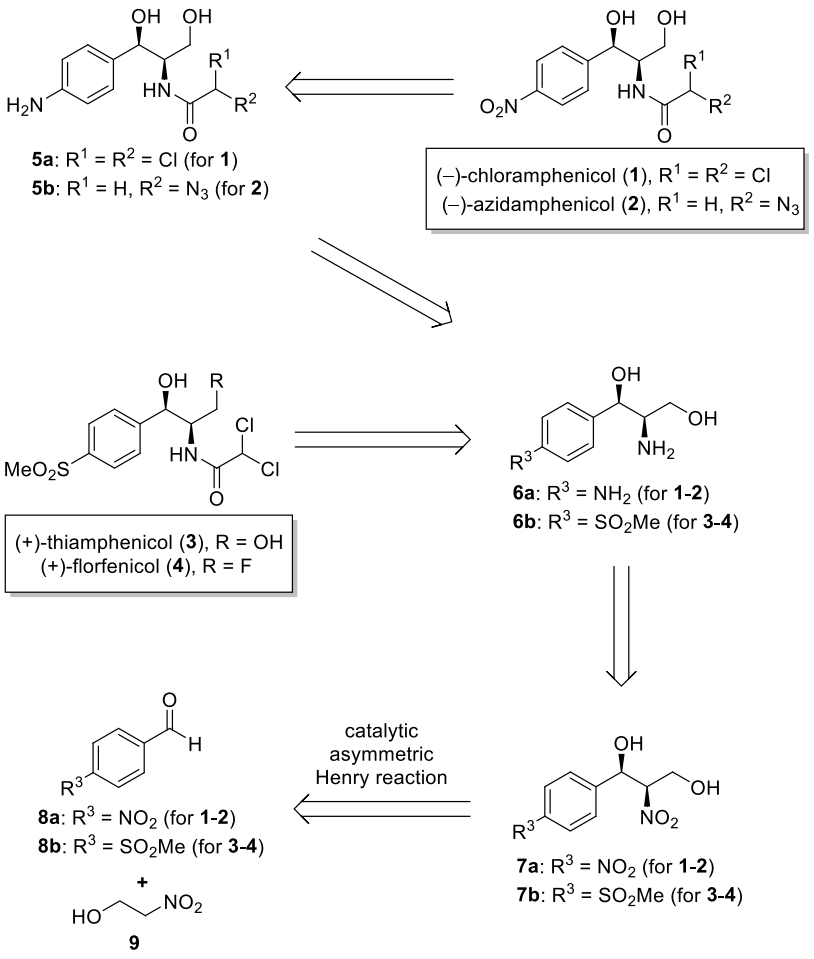
Figure 1. Structure of amphenicol antibiotics (**1**−**4**).

Received: May 13, 2021

Scheme 1. Previous Asymmetric Approaches Toward Amphenicol Antibiotics (1−4)



Scheme 2. Retrosynthetic Analysis of 1−4

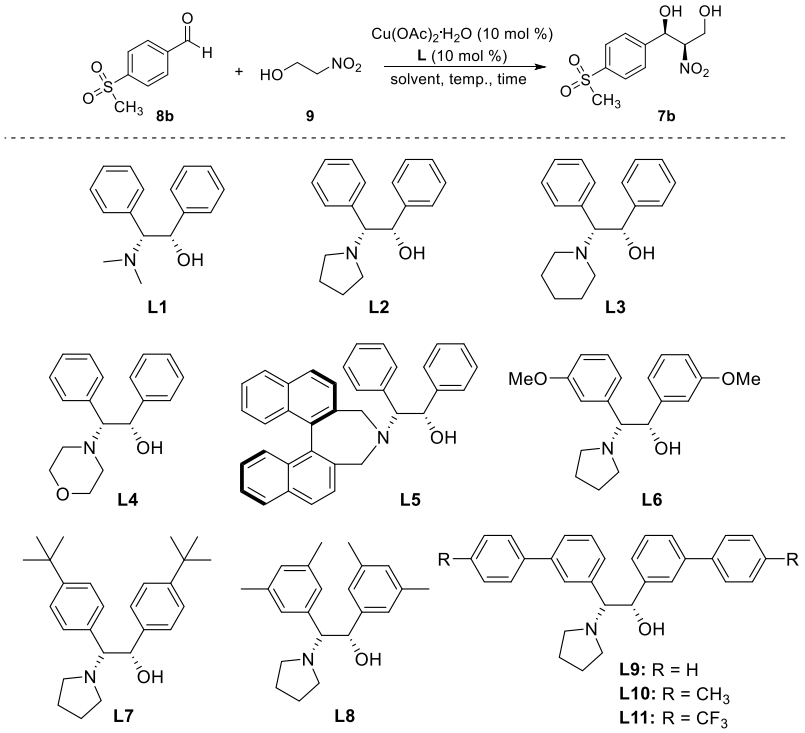


catalytic halohydroxylation,[5b] Wulff's catalytic asymmetric aziridination,[5c] Rao[5d] and Wu's[5e] catalytic Sharpless epoxidation, Dixon's silver-catalyzed isocyanoacetate aldol cyclization,[5f] Ratovelomanana-Vidal's Ruthenium,[5g] and Chen's[5h] enzyme-catalyzed dynamic reductive kinetic resolution, Lin's enzyme-catalyzed hydrocyanation,[5i] etc (Scheme 1). However, synthetic efficiency and stereoselectivities still need to be improved from the viewpoint of practical synthesis.

Our group has also developed several new synthetic strategies, including Sharpless[6] and vanadium-catalyzed[7] asymmetric epoxidation of allylic alcohol, Sharpless asymmetric dihydroxylation of acrylic esters,[8] ruthenium-catalyzed asymmetric transfer hydrogenation/dynamic kinetic resolution of *N*-Boc-

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions on the Copper-Catalyzed Asymmetric Henry Reaction of 8b with 9[a]



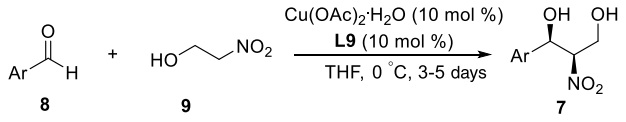
Entry	L	Solvent	Time (h)	Yield[b] (%)	*dr*[c] *syn*/*anti*	*ee*[c] (%)
1	**L1**	THF	24	68	73:27	97
2	**L2**	THF	24	76	75:25	97
3	**L3**	THF	24	95	70:30	81
4	**L4**	THF	24	NR	-	-
5	**L5**	THF	24	36	72:28	22
6	**L6**	THF	24	73	70:30	96
7	**L7**	THF	24	75	71:29	92
8	**L8**	THF	24	78	76:24	95
9	**L9**	THF	24	81	80:20	97
10	**L10**	THF	24	78	78:22	97
11	**L11**	THF	24	77	76:24	96
12	**L9**	CH_3CN	24	90	69:31	87
13	**L9**	DCM	24	91	62:38	72
14	**L9**	DCE	24	92	76:24	87
15	**L9**	DMF	24	95	66:33	5
16[d]	**L9**	THF	24	23	97:3	97
17[e]	**L9**	THF	24	20	86:14	96
18[d,f]	**L9**	THF	72	98	97:3	97
19[d,f,g]	**L9**	THF	120	96	94:6	97

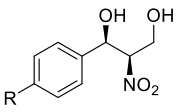
[a]Unless noted otherwise, reactions were performed with **8b** (0.2 mmol), **9** (0.6 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), and **L** (10 mol %) in a solvent (0.8 mL) at 25 °C for 24 h. [b]Isolated yield. [c]The *syn*/*anti* ratio and ee determined by chiral HPLC. [d]At 0 °C. [e]At −5 °C. [f]**9** (4.0 equiv) in 0.3 mL THF. [g]With $Cu(OAc)_2·H_2O$ (5 mol %), **L9** (5 mol %).

α-amino-*β*-ketoester,[9] thiourea-catalyzed asymmetric aldol reaction of aldehydes with isocyanatomalonate,[10] catalytic asymmetric Wulff-type aziridination of benzhydryl imine for the assembly of the *syn*-(1*R*,2*R*)-2-amino-1,3-diol framework,[11] and applied these techniques to the enantioselective synthesis of these amphenicol antibiotics. However, a significant drawback

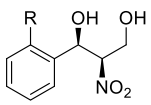
https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope of Aryl Aldehydes[a]

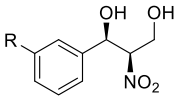




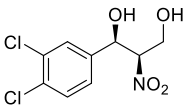
7a, R = NO_2, 98%[b], *syn*/*anti* = 90:10, 95% *ee*
7b, R = SO_2Me, 98%, *syn*/*anti* = 97:3, 97% *ee*
7c, R = F, 96%, *syn*/*anti* = 94:6, 99% *ee*
7d, R = Cl, 93%, syn/anti = 94:6, 98% *ee*
7e, R = Br, 87%, *syn*/*anti* = 87:13, 97% *ee*
7f, R = CF_3, 99%, *syn*/*anti* = 89:11, 97% *ee*
7g, R = CN, 98%, *syn*/*anti* = 92:8, 96% *ee*
7h, R = H, 85%, *syn*/*anti* = 94:6, 99% *ee*
7i, R = Me, 82%, *syn*/*anti* =88:12, 99% *ee*
7j, R = OMe, 81%, *syn*/*anti* = 93:7, 96% *ee*
7k, R = SMe, 94%, *syn*/*anti* =89:11, 98% *ee*
7l, R = Ph, 95%, *syn*/*anti* = 93:7, 99% *ee*
7m, R = OAc, 76%, *syn*/*anti* = 94:6, 98% *ee*



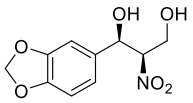
7n, R = F, 98%, *syn*/*anti* = 96:4, 99% ee
7o, R = Cl, 96%, *syn*/*anti* = 92:8, 97% ee
7p, R = Br, 98%, *syn*/*anti* = 92:8, 96% ee
7q, R = Me, 81%, *syn*/*anti* = 91:9, 99% ee



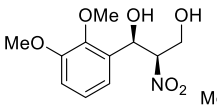
7r, R = Cl, 97%, *syn*/*anti* = 95:5, 99% *ee*
7s, R = Br, 98%, *syn*/*anti* = 95:5, 99% *ee*
7t, R = Me, 88%, *syn*/*anti* = 95:5, 99% *ee*



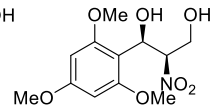
7u
96%
syn/*anti* = 91:9
97% *ee*



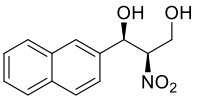
7v
82%
syn/*anti* = 82:18
95% *ee*



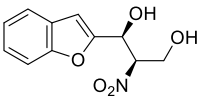
7w
93%
syn/*anti* = 93:7
99% *ee*



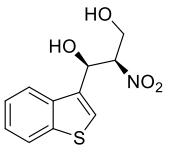
7x
98%
syn/*anti* = 99:1
>99% *ee*



7y
82%
syn/*anti* = 89:11
98% *ee*



7z
98%
syn/*anti* = 90:10
97% *ee*



7aa
92%
syn/*anti* = 95:5
98% *ee*

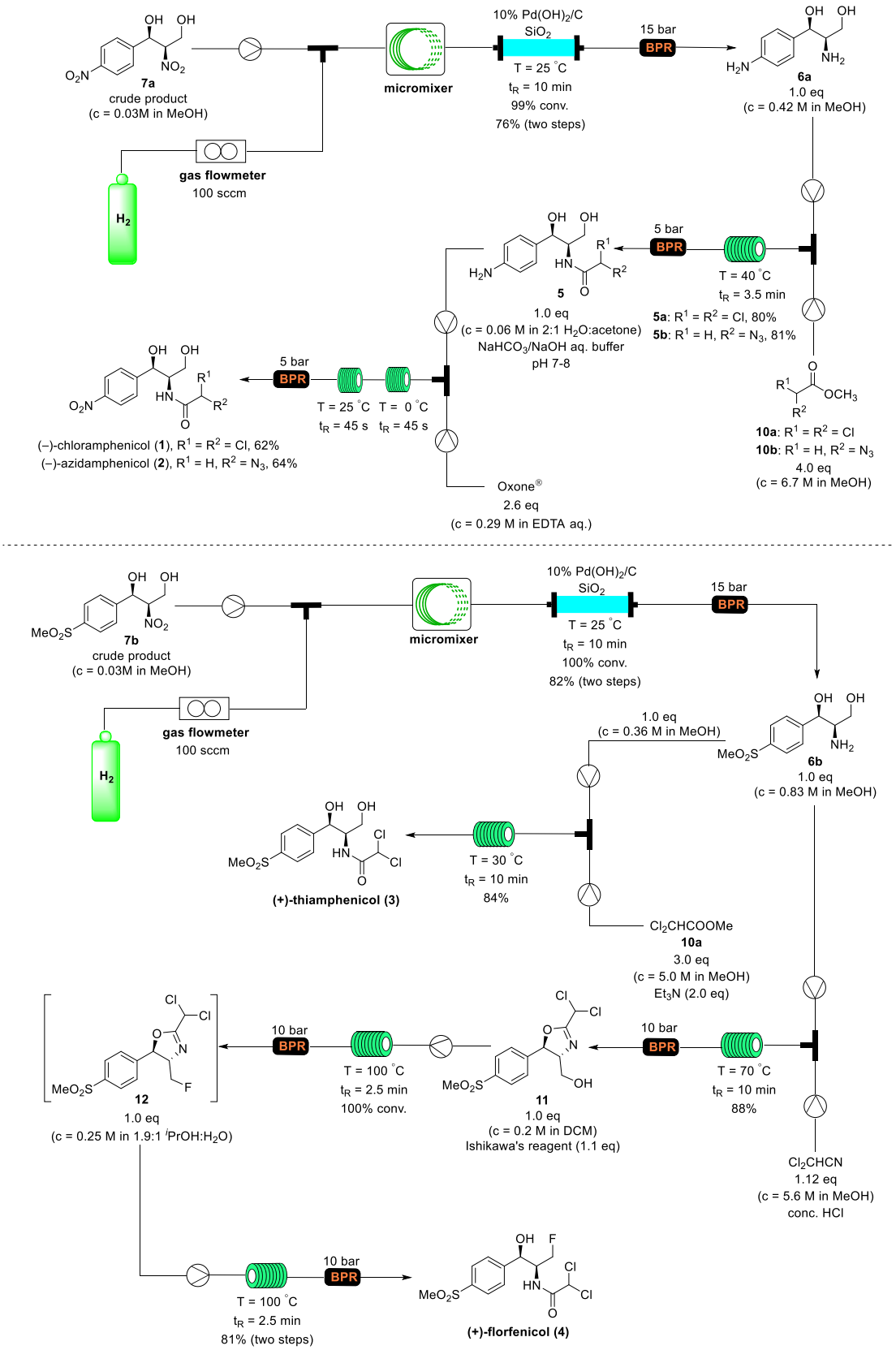
[a]Reaction conditions: **8** (1.0 mmol), **9** (4.0 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), and **L9** (10 mol %) in THF (1.5 mL) at 0 °C for 72−120 h. The isolated yield was provided. The *syn*/*anti* ratio and the ee value were determined by chiral HPLC analysis. [b]Conversion yield determined by HPLC.

associated with these platforms is the synthetic difficulty in the stereochemical control of the *syn*-relationship between the *C*-1 and *C*-2 stereocenters during the construction of highly functionalized chiral scaffolds in their structures. To resolve this problem, it would be desirable to establish a practical and flexible strategy (i.e., short steps, facile reaction conditions, cheap commercially available starting materials, and excellent stereoselectivity) leading to the asymmetric synthesis of all of the amphenicol antibiotics and their analogues in this family bearing *syn*-2-amino-1,3-diol with vicinal stereocenters.

An attractive alternative, especially considering atom and step economy,[12] would be via Chen's ligand-controlled copper(II)-catalyzed diastereo- and enantioselective nitroaldol (Henry reaction) process that could open the opportunity for the construction of the *syn*-2-nitro-1,3-diol unit possessing vicinal stereocenters.[13] Although Chen's method is limited to only aliphatic substrates, this elegant catalytic *syn*-selective enantioselective nitroaldol approach caught our attention. Had this been the case, a catalytic *syn*-selective enantioselective nitroaldol reaction[14] could be expected, allowing access to the *syn*-2-nitro-1,3-diol motif with two adjacent stereocenters required for the enantioselective synthesis of (−)-chloramphenicol (**1**), (−)-azidamphenicol (**2**), (+)-thiamphenicol (**3**), and (+)-florfenicol (**4**). Based on this idea, a retrosynthetic analysis of **1**−**4** is depicted in Scheme 2. We envisioned that *syn*-2-amino-1,3-diols **6a** and **6b** are the advanced intermediates for the enantioselective synthesis of amphenicol antibiotics **1**−**2** and **3**−**4**, which can be accessed from the corresponding *syn*-2-nitro-1,3-diols **7a** and **7b** via catalytic hydrogenation under continuous flow conditions, respectively. To access compounds **7a** and **7b**, a

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Completion of Enantioselective Synthesis of Amphenicol Antibiotics (1−4) in Continuous Flow



challenging *syn*-selective and enantioselective Henry reaction of 4-nitrobenzaldehyde (**8a**) or 4-methylsulfonyl benzaldehyde (**8b**) with 2-nitroethanol (**9**), three compounds being commercially available, would wait for us to achieve.

RESULTS AND DISCUSSION

Having designed the novel route to amphenicol antibiotics (**1**−**4**), we first investigated the copper(II)-catalyzed asymmetric

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Henry reaction of 4-methylsulfonyl benzaldehyde (**8b**) and 2-nitroethanol (**9**), and the results are summarized in Table 1. The desired *syn*-adduct product **7b** was obtained in 68% yield and with a moderate dr (*syn*/*anti*) of 73:27 and an excellent enantioselectivity of 97% ee when using 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 10 mol % of noncyclic chiral amino alcohol ligand **L1**, commonly used in copper-catalyzed asymmetric Henry reactions, in THF at room temperature for 24 h (entry 1). Other ligands for the Cu(II) catalyst were then investigated, including the known[13,15] 1,2-nonsubstituted diphenyl β-amino alcohol ligands **L2**−**L5** and our newly developed disubstituted-1,2-diphenyl amino alcohol ligands **L6** and **L7**, tetrasubstituted-1,2-diphenyl amino alcohol ligand **L8**, and 1,2-di-biphenyl-substituted amino alcohol ligands **L9**−**L11** (see the Supporting Information for details). The reaction proceeded smoothly with the use of pyrrolidine-derived ligand **L2**, giving a result similar to the case of using ligand **L1** (76%, *syn*/*anti* = 75:25, 97% ee) (entry 2). The yield could be improved to 95% using piperidine-derived ligand **L3** in place of ligand **L2**, but a poor enantioselectivity was observed (entry 3). The ligand **L4** bearing a morpholino group showed no reactivity under the reaction conditions (entry 4). The reaction with the ligand **L5**, derived from (*R*)-binaphthylazepine, was also less effective, providing *syn*-adduct **7b** in only 36% yield with a poor enantioselectivity of 22% ee (entry 5). Subsequent investigations were focused on the pyrrolidine-derived chiral ligands **L6**−**L11**, which feature a 1,2-di or tetrasubstituted diphenyl group and a 1,2-dibiphenyl group bearing different electronic and steric properties. It was found that all of the reactions using **L6**−**L11** as the ligands produced *syn*-adduct **7b** in good yields with good *syn*-selectivity and excellent enantioselectivity (entries 6−11). The reaction using **L9** as the ligand showed the best result, leading to the desired product **7b** in 81% yield with 80:20 dr (*syn*/*anti*) and 97% ee (entry 9). Further optimization of reaction conditions indicated that some reaction parameters, including solvent, temperature, the molar ratio of **8b** to **9**, concentration, and the catalyst loading amount, have an impact on this Henry reaction. The use of other solvents, such as MeCN, DCM, DCE, and DMF, could improve the yield (90−95%), but the poor diastereo- and enantioselectivities were observed (entries 12−15), and THF remained the best choice for this reaction. Notably, the diastereoselectivity was remarkably increased to 97:3 (*syn*/*anti*), albeit with 23% yield without affecting the enantioselectivity when the reaction proceeded at 0 °C (entry 16). Further decreasing the reaction temperature to −5 °C, slightly lower yield and diastereo- and enantioselectivities were observed (entry 17). Furthermore, increasing the loading of **9** to 4.0 equivalents relative to that of **8b** and concentration from 0.25 M to 0.67 M under the identical reaction conditions (THF, 0 °C) led to a 98% yield of *syn*-adduct **7b** with 97:3 dr (*syn*/*anti*) and 97% ee after prolonged reaction time (3 days, entry 18). Interestingly, when the catalyst loading was reduced to 5 mol %, the same result could be obtained (96% yield, 94:6 dr, 97% ee), albeit with an even longer reaction time (5 days, entry 19). With a systematic survey, the optimal reaction conditions were determined, as shown in entry 18 of Table 1.

With the optimized reaction conditions in hand, the substituted scope of the aryl aldehydes was then investigated, and the results are shown in Table 2. A variety of benzaldehydes (**8a**−**8t**) bearing monosubstituents at any position of the phenyl ring were initially surveyed. Both electron-withdrawing and donating groups were compatible with this transformation, and a diverse array of functional groups, such as halogen, methylsulfonyl, nitro, trifluoromethyl, nitrile, ester, methoxy, and methylthio, were tolerated under the reaction conditions to give the desired products (**7a**−**7t**) in good to excellent yields (76−99%) with good to excellent diastereoselectivities (87:13 to 97:3 dr) and excellent enantioselectivities (95−99% ee). For benzaldehyde with disubstituents at any position of the phenyl ring, the reaction proceeded smoothly to generate **7u**−**7w** in good to excellent yields (82−96%) with good to excellent diastereoselectivities (82:18 to 93:7 dr), and excellent enantioselectivities (95−99% ee). These results indicated that the electronic properties and steric hindrance exert little effect on this reaction. The trisubstituted benzaldehyde, 2,4,6-trimethoxybenzaldehyde (**8x**), was also suitable for this reaction, delivering the desired *syn*-adduct product **7x** in 98% yield with excellent diastereo- and enantioselectivity (99:1 dr, >99% ee). In addition to benzaldehydes, fused aryl (2-naphthyl) and fused heterocyclic aldehydes (**8y**, **8z**, and **8aa**) were also good substrates for this reaction providing the corresponding products (**7y**−**7aa**) with high efficiency (82−98% yield, 89:11 to 95:5 dr, 97−98% ee).

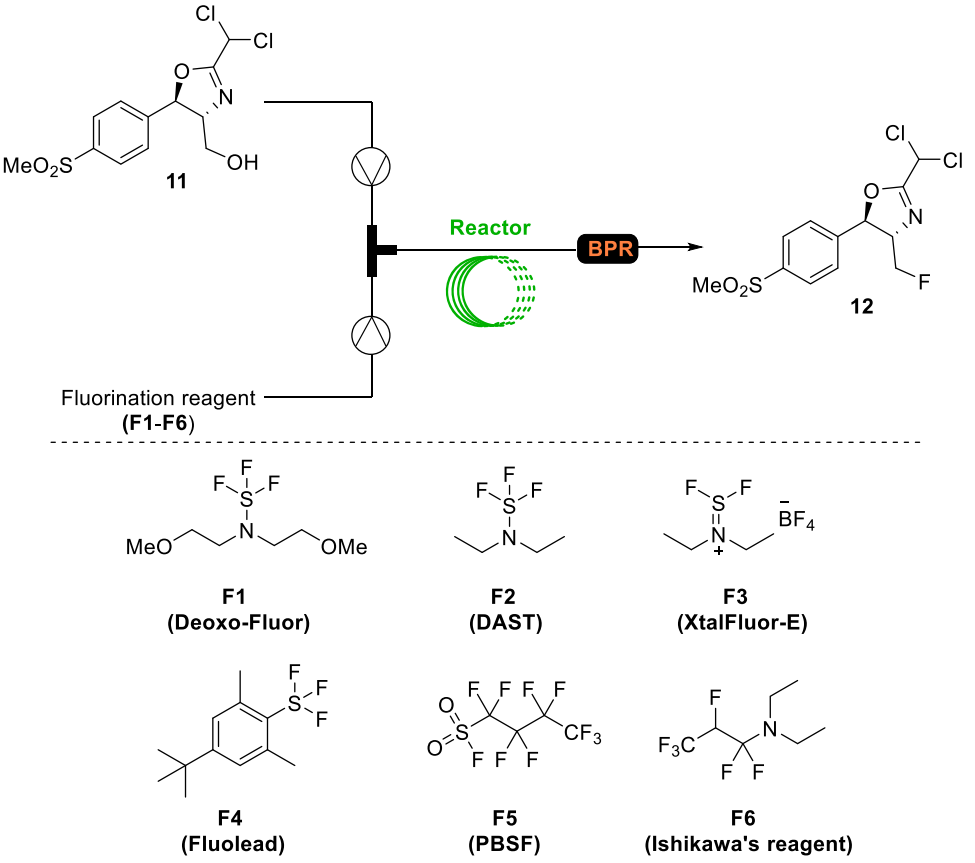
After the synthetic route to access the *syn*-2-nitro-1,3-diols has been established, we proceeded to develop multigram-scale continuous-flow processes for the enantioselective synthesis of amphenicol antibiotics (**1**−**4**) (Scheme 3).[16] We began with *syn*-adduct **7a** (95% ee) and *syn*-adduct **7b** (97% ee) in our endeavor to develop the continuous-flow process. First, the continuous flow hydrogenation[17] of crude **7a** was conducted in a fixed bed reactor (MF-200, Shenzhen E-Zheng Tech Co., Ltd.) containing 10% of $Pd(OH)_2/C$ dispersed in SiO_2 (5 mL internal volume) at 25 °C and 15 bar back-pressure, giving *syn*-2- amino-1,3-diol **6a** in 76% yield in a residence time of 10 min. Remarkably, the catalytic system was found to be stable at room temperature for at least 10 days without reducing the catalytic activity. The *syn*-2-amino-1,3-diol **6a** was combined with methyl dichloroacetate (**10a**) and methyl 2-azidoacetate (**10b**) pumped, respectively, into a 1.0 mL PTFE reactor coil (i.d. = 0.8 mm) at 40 °C with a residence time of 3.5 min to afford the corresponding **5a** and **5b** in 80% yield and 81% yield. The solution of **5a** in H_2O/acetone and aqueous $NaHCO_3$/NaOH buffer was combined at a T-mixer with a stream of oxone in aqueous EDTA, and the oxidation reaction proceeded smoothly in a PTFE reactor coil with a residence time of 1.5 min to furnish (−)-chloramphenicol (**1**) in 62% yield after recrystallization from AcOEt/petroleum ether. It is noted that the flow protocol was optimized by operating the first half of the flow reactor at 0 °C, while the second half of the flow reactor at room temperature.

In addition to (−)-chloramphenicol (**1**), (−)-azidamphenicol (**2**) could also be efficiently prepared in 64% yield from **5b** under exactly the same reaction conditions using the same flow setup.

Next, we continued with continuous flow synthesis of (+)-thiamphenicol (**3**) and (+)-florfenicol (**4**). At the outset, catalytic hydrogenation of **7b** delivered the desired product **6b** in 82% yield under the same flow conditions. This flow reaction could be continuously operated for over 72 h without any clogging issues along with a throughput of 0.18 $g \cdot h^{-1}$ (i.e., 4.3 $g \cdot day^{-1}$). The *syn*-2-amino-1,3-diol **6b** could serve as a common intermediate for the asymmetric synthesis of target molecules (**3** and **4**) by subsequent transformations. A methanol solution of **6b**, methyl dichloroacetate (**10a**), and Et_3N was streamed through a PTFE reactor coil, and the acylation was found to proceed at 30 °C with 10 min residence time, affording (+)-thiamphenicol (**3**) in 84% yield.

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. Optimization of the Fluorination Reaction Conditions in Flow[a]



entry	conditions	yield[b] (%)
1	Deoxo-Fluor (2.0 equiv), DCM, 25 °C, 10 min	52
2	DAST (2.0 equiv), THF, 25 °C, 10 min	36
3	XtalFluor-E (2.0 equiv), DCM, 25 °C, 10 min	20
4	Fluolead (2.0 equiv), DCM, 25 °C, 10 min	24
5	PBSF (1.5 equiv), Et_3N (3.0 equiv), $Et_3N{\cdot}3HF$ (3.0 equiv), THF, 40 °C, 10 bar, 40 min	89
6	Ishikawa's reagent (1.1 equiv), DCM, 100 °C, 10 bar, 2.5 min	95

[a]Reaction conditions: **11** (1.0 mmol) and solvent (5 mL) in flow. [b]Isolated yield.

For the preparation of (+)-florfenicol (**4**), a solution of **6b** in MeOH and a solution of dichloroacetonitrile in MeOH with a catalytic amount of conc. HCl were pumped separately into a reactor coil using two syringe pumps at 70 °C and 10 bar back-pressure with a residence time of 10 min to afford the oxazolyl alcohol **11** in 88% yield. With access to the oxazolyl alcohol **11**, the introduction of fluorine functionality to **11** in flow was at hand (Table 3). Initially, oxazolyl alcohol **11** was subjected to fluorination with Deoxo-Fluor (**F1**) into a reactor coil at 25 °C with 10 min residence time, which generated 52% yield of the desired oxazolyl fluoride **12**, along with large amounts of unreacted **11** (entry 1). Further optimization studies were undertaken for this fluorination reaction. Other fluorination reagents (**F2**−**F6**) under reaction conditions illustrated in entries 2−6 of Table 3 were investigated. To our dismay, DAST (**F2**), XtalFluor-E (**F3**), and Fluolead (**F4**) only showed poor reactivity (entries 2−4). In contrast, PBSF (**F5**) performed better to provide the desired product **12** in 89% yield with a residence time of 40 min (entry 5). Further screening indicated that Ishikawa's reagent (**F6**) under flow conditions (100 °C, 10 bar back-pressure, and 2.5 min residence time) was the best fluorinating agent and cleanly produced the corresponding product **12** in excellent yield (95%, entry 6). Finally, the crude product **12** was then dissolved in $^{i}PrOH/H_2O$ and subsequently streamed into another reactor coil at 100 °C and 10 bar back-pressure. This flow protocol achieved 81% yield of (+)-florfenicol (**4**) in a residence time of 2.5 min.

CONCLUSIONS

In conclusion, we have successfully developed a unique and general strategy that allows the enantioselective synthesis of the amphenicol antibiotics, including (−)-chloramphenicol (**1**), (−)-azidamphenicol (**2**), and (+)-thiamphenicol (**3**) and its 3-fluoro derivative, (+)-florfenicol (**4**), without the requirement for any protecting chemistry. The novel synthetic strategy was enabled by the key copper(II)-chiral biphenyl-substituted amino alcohol complex catalyzed Henry reaction, which allows efficient and high diastereo- and enantioselective construction of the common *syn*-2-amino-1,3-diol moiety. Our strategy can provide a platform for the straightforward and asymmetric synthesis of other pharmacologically important molecules and biologically active natural products containing the *syn*-2-amino-1,3-diol subunit with two vicinal stereocenters.

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

EXPERIMENTAL SECTION

General Information. All aldehydes (**8a**−**8z** and **8aa**), 2-nitroethanol (**9**), and solvents were commercially available. Amino alcohol ligands **L1**−**L5** were prepared according to the literature procedures.[13,15] NMR data (^{1}H, ^{13}C, and ^{19}F) were recorded on Bruker Avance III 600 and 400 spectrometers. Chemical shifts were referred to as TMS. HRMS were measured on a Bruker micro TOF Q III. Ultraviolet light (UV) detection was monitored at 254 nm. The procedure of continuous flow was monitored by thin-layer chromatography (TLC) and LC−MS (Agilent 6545 LC/Q-TOF, Agilent 1260 Infinity II, Eclipse Plus C18, RRHD 1.8 μm, 2.1 × 50 mm^2). Column chromatography was performed on silica gel (200−300 mesh), eluting with dichloromethane/methanol and petroleum ether/ethyl acetate. Melting points were measured on an SRS-optic melting point apparatus. In each case, *syn*/*anti* ratio and enantiomeric ratio were determined by HPLC analysis on a chiral column in comparison with authentic racemate, using a Daicel Chiralpak IC Column (250 × 4.6 mm^2), Chiralpak AS-H Column (250 × 4.6 mm^2), or Chiralpak AD-H Column (250 × 4.6 mm^2).

General Procedure for the Racemic Henry Reactions. To a mixture of aldehydes **8** (1 mmol, 1.0 equiv) and 2-nitroethanol **9** (3 mmol, 3.0 equiv) in THF (2 mL) was added TBAF (1 mL, 1.0 equiv, 1 M solution in THF) dropwise at room temperature and the mixture was stirred at room temperature for 36 h. Water (2 mL) was added, and the aqueous phase was extracted twice with ethyl acetate (2 × 3 mL). The organic layer was combined and washed with brine (3 mL), then dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:2) to give the corresponding racemic products ***rac*-7**.

General Procedure for the Asymmetric Henry Reactions. A solution of $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 10 mol %) and **L9** (0.1 mol, 10 mol %) in THF (1.5 mL) was stirred for 1 h at room temperature. Then, aldehyde **8** (1.0 mmol, 1.0 equiv) and 2-nitroethanol **9** (4.0 mmol, 4.0 equiv) were added into the reaction flask at 0 °C. The mixture was stirred for 72−120 h at 0 °C and then quenched with 1 M HCl (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was combined and washed with brine (5 mL). The organic phase was dried with Na_2SO_4 and evaporated in a vacuum. The resulting residue was purified by silica gel chromatography (DCM/MeOH = 50:1) to give the corresponding *syn*-2-nitro-1,3-diols **7**.

(1R,2R)-1-(4-(Methylsulfonyl)phenyl)-2-nitropropane-1,3-diol (***7b***). White solid, mp 136−138 °C, 60 h, 269.8 mg, 98% yield, *syn*/*anti* = 97:3; ^{1}H NMR (400 MHz, DMSO): δ 7.93 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 6.35 (d, J = 4.8 Hz, 1H), 5.28 (dd, J_1 = 6.4 Hz, J_2 = 4.4 Hz, 1H), 5.06 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1H), 4.80 (td, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.84−3.77 (m, 1H), 3.25 (dt, J_1 = 12.4 Hz, J_2 = 4.0 Hz, 1H), 3.21 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 146.5, 141.1, 128.4, 127.6, 95.4, 71.2, 60.5, 43.9 ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_6S$ + Na 298.0361, found 298.0362; $[\alpha]_D^{25}$ = −32.6 (c = 0.29, EtOH). The enantiomeric excess of product **7b** was determined by chiral HPLC: 97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 65/35, flow rate: 0.7 mL/min, T = 30 °C, 210 nm), *anti* isomer: t_{major} = 17.918 min, t_{minor} = 20.068 min; *syn* isomer: t_{major} = 30.064 min, t_{minor} = 22.175 min.

(1R,2R)-1-(4-Fluorophenyl)-2-nitropropane-1,3-diol (***7c***). Colorless oil, 84 h, 96% yield, 206.6 mg, *syn*/*anti* = 94:6; ^{1}H NMR (400 MHz, CD_3OD): δ 7.46−7.38 (m, 2H), 7.15−7.05 (m, 2H), 5.02 (d, J = 7.2 Hz, 1H, *anti*), 5.01 (d, J = 9.2 Hz, 1H, *syn*), 4.79 (td, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 4.18 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.03 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.82 (dd, J_1 = 12.0 Hz, J_2 = 9.2 Hz, 1H, *syn*), 3.38 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 162.8 (d, J = 244.4 Hz, *syn*), 162.7 (d, J = 243.8 Hz, *anti*), 135.9 (d, J = 3.2 Hz, *anti*), 135.7 (d, J = 3.1 Hz, *syn*), 128.6 (d, J = 8.2 Hz, *syn*), 128.3 (d, J = 243.8 Hz, *anti*), 115.1 (d, J = 21.8 Hz, *syn*), 114.8 (d, J = 21.8 Hz, *anti*), 95.1 (*syn*), 94.4 (*anti*), 71.6 (*anti*), 71.5 (*syn*), 60.4 (*syn*), 60.1 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{10}FNO_4$+Na 238.0492, found 238.0497; $[\alpha]_D^{25}$ = −30.9 (c = 0.61, EtOH). The enantiomeric excess of product **7c** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 22.550 min, t_{minor} = 27.981 min; *syn* isomer: t_{major} = 41.961 min, t_{minor} = 55.233 min.

(1R,2R)-1-(4-Chlorophenyl)-2-nitropropane-1,3-diol (***7d***). Pale yellow oil, 108 h, 93% yield, 215.4 mg, *syn*/*anti* = 94:6; ^{1}H NMR (400 MHz, CD_3OD): δ 7.40−7.35 (m, 4H), 5.02 (d, J = 9.2 Hz, 1H), 4.82−4.76 (m, 1H), 3.83 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H), 3.41 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 139.6, 135.2, 129.7, 129.4, 96.1, 72.6, 61.5 ppm. ESI HRMS: calcd. for $C_9H_{10}ClNO_4$+Na 254.0196, found 254.0192; $[\alpha]_D^{25}$ = −21.9 (c =1.76, EtOH). The enantiomeric excess of product **7d** was determined by chiral HPLC: 98% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 9.847 min, t_{minor} = 11.750 min; *syn* isomer: t_{major} = 16.376 min, t_{minor} = 19.956 min.

(1R,2R)-1-(4-Bromophenyl)-2-nitropropane-1,3-diol (***7e***). Pale yellow oil, 108 h, 87% yield, 240.2 mg, *syn*/*anti* = 87:13; ^{1}H NMR (400 MHz, CD_3OD): δ 7.54 (d, J = 8.4 Hz, 2H, *syn*), 7.50 (d, J = 8.4 Hz, 2H, *anti*), 7.33 (d, J = 8.4 Hz, 2H, *syn*), 7.30 (d, J = 8.4 Hz, 2H, *anti*), 4.99 (d, J = 9.2 Hz, 1H), 4.77 (td, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 4.18 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 3.99 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.82 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *syn*), 3.40 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 139.2 (*anti*), 138.9 (*syn*), 131.5 (*syn*), 131.2 (*anti*), 128.5 (*syn*), 128.2 (*anti*), 122.1 (*syn*), 121.8 (*anti*), 94.9 (*syn*), 94.2 (*anti*), 71.6 (*anti*), 71.5 (*syn*), 60.3 (*syn*), 59.9 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{10}BrNO_4$+Na 297.9691, found 297.9695; $[\alpha]_D^{25}$ = −15.3 (c = 0.77, EtOH). The enantiomeric excess of product **7e** was determined by chiral HPLC: 97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 33.386 min, t_{minor} = 41.268 min; *syn* isomer: t_{major} = 64.533 min, t_{minor} = 80.172 min.

(1R,2R)-2-Nitro-1-(4-(trifluoromethyl)phenyl)propane-1,3-diol (***7f***). Colorless oil, 84 h, 262.5 mg, 99% yield, *syn*/*anti* = 89:11; ^{1}H NMR (400 MHz, CD_3OD): δ 7.70 (d, J = 8.0 Hz, 2H, *syn*), 7.66 (d, J = 8.4 Hz, 2H, *anti*), 7.62 (d, J = 8.0 Hz, 2H, *syn*), 7.59 (d, J = 8.0 Hz, 2H, *anti*), 5.13 (d, J = 9.2 Hz, 1H), 4.82 (td, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 4.21 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.00 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *anti*), 3.86 (dd, J_1 = 12.0 Hz, J_2 = 8.8 Hz, 1H, *syn*), 3.45 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 142.9 (*anti*), 142.6 (*syn*), 128.8 (q, J = 32 Hz), 125.8 (*syn*), 125.4 (*anti*), 123.7 (q, J = 4 Hz, *syn*), 123.4 (q, J = 4 Hz, *anti*), 122.6 (q, J = 269 Hz), 93.2 (*syn*), 92.6 (*anti*), 70.0 (*anti*), 69.9 (*syn*), 58.7 (*syn*), 58.2 (*anti*) ppm. ESI HRMS: calcd. for $C_{10}H_{10}F_3NO_4$ + Na 288.0460, found 288.0465; $[\alpha]_D^{25}$ = −14.7 (c = 2.32, EtOH). The enantiomeric excess of product **7f** was determined by chiral HPLC: 97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 6.902 min, t_{minor} = 7.896 min; *syn* isomer: t_{major} = 10.885 min, t_{minor} = 12.577 min.

4-((1R,2R)-1,3-Dihydroxy-2-nitropropyl)benzonitrile (***7g***). White solid, mp 110−111 °C, 60 h, 217.8 mg, 98% yield, *syn*/*anti* = 92:8; ^{1}H NMR (400 MHz, CD_3OD): δ 7.77−7.74 (m, 2H), 7.63−7.61 (m, 2H), 5.14 (d, J = 8.8 Hz, 1H), 4.83−4.78 (m, 1H), 3.86 (dd, J_1 = 12.4 Hz, J_2 = 8.8 Hz, 1H), 3.48 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 143.8, 130.7, 126.1, 116.5, 110.5, 92.9, 69.8, 58.7 ppm. ESI HRMS: calcd. for $C_{10}H_{10}N_2O_4$ + Na 245.0538, found 245.0569; $[\alpha]_D^{25}$ = −36.4 (*c* = 0.45, EtOH). The enantiomeric excess of product **7g** was determined by chiral HPLC: 96% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 0.8 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 33.155 min, t_{minor} = 35.837 min; *syn* isomer: t_{major} = 59.506 min, t_{minor} = 50.737 min.

(1R,2R)-2-Nitro-1-phenylpropane-1,3-diol (***7h***). Pale yellow oil, 132 h, 167.6 mg, 85% yield, *syn*/*anti* = 94:6; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 5H), 5.46 (t, J = 4.4 Hz, 1H, *anti*), 5.24 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H, *syn*), 4.81−4.76 (m, 1H, *syn*), 4.70−4.66 (m, 1H, *anti*), 4.25−4.07 (m, 2H, *anti*), 3.83−3.72 (m, 2H, *syn*), 3.21 (d, J = 4.8 Hz, 1H, *anti*), 2.85 (d, J = 4.0 Hz, 1H, *syn*), 2.61 (t, J = 7.2 Hz, 1H, *anti*), 2.28 (d, J = 6.0 Hz, 1H, *syn*) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.2 (*anti*), 138.0 (*syn*), 129.4 (*syn*), 129.2 (*syn*), 129.0 (*anti*), 128.9 (*anti*), 126.6 (*syn*), 125.9 (*anti*), 93.8 (*syn*), 91.9 (*anti*), 73.4 (*anti*), 72.6 (*syn*), 61.3 (*syn*), 60.0 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{11}NO_4$+Na 220.0586, found 220.0582; $[\alpha]_D^{25}$ = 2.0 (*c* = 0.79,

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

EtOH). The enantiomeric excess of product **7h** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 13.511 min, t_{minor} = 15.645 min; *syn* isomer: t_{major} = 20.455 min, t_{minor} = 27.789 min.

*(1R,2R)-2-Nitro-1-(p-tolyl)propane-1,3-diol (**7i**).* Pale yellow oil, 156 h, 173.2 mg, 82% yield, *syn*/*anti* = 88:12; ^{1}H NMR (400 MHz, CD_3OD): δ 7.29−7.16 (m, 4H), 4.99 (d, J = 7.2 Hz, 1H, *anti*), 4.94 (d, J = 9.6 Hz, 1H, *syn*), 4.80 (td, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 4.20 (dd, J_1 = 12.4 Hz, J_2 = 9.6 Hz, 1H, *anti*), 4.05−4.00 (m, 1H, *anti*), 3.82 (dd, J_1 = 12.4 Hz, J_2 = 10.0 Hz, 1H, *syn*), 3.34 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H, *syn*), 2.34 (s, 3H, *syn*), 2.32 (s, 3H, *anti*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ138.5 (*syn*), 138.0 (*anti*), 136.8 (*anti*), 136.5 (*syn*), 129.1 (*syn*), 128.7 (*anti*), 126.5 (*syn*), 126.1 (*anti*), 95.3 (*syn*), 94.5 (*anti*), 72.2, 60.5 (*syn*), 60.1 (*anti*), 19.8 (*syn*), 19.8 (*anti*) ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_4$+Na 234.0742, found 234.0738; $[\alpha]_D^{25}$ = −11.4 (c = 0.56, EtOH). The enantiomeric excess of product **7i** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 14.779 min, t_{minor} = 18.756 min; *syn* isomer: t_{major} = 24.737 min, t_{minor} = 35.048 min.

*(1R,2R)-1-(4-Methoxyphenyl)-2-nitropropane-1,3-diol (**7j**).* Colorless oil, 144 h, 184 mg, 81% yield, *syn*/*anti* = 93:7; ^{1}H NMR (400 MHz, CD_3OD): δ 7.34−7.32 (m, 2H), 6.97−6.95 (m, 2H), 4.94 (d, J = 9.6 Hz, 1H), 4.84−4.78 (m, 1H), 3.83−3.79 (m, 4H), 3.36 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 161.3 (*syn*), 161.0 (*anti*), 132.9 (*anti*), 132.6 (*syn*), 129.0 (*syn*), 128.7 (*anti*), 115.0 (*syn*), 114.6 (*anti*), 96.6 (*syn*), 95.7 (*anti*), 73.2 (*anti*), 73.1 (*syn*), 61.7 (*syn*), 61.4 (*anti*), 56.0 (*anti*), 55.5 (*syn*) ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_5$+Na 250.0691, found 250.0683; $[\alpha]_D^{25}$ = −6.9 (c = 0.79, EtOH). The enantiomeric excess of product **7j** was determined by chiral HPLC: 96% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 19.900 min, t_{minor} = 25.022 min; *syn* isomer: t_{major} = 36.504 min, t_{minor} = 46.255 min.

*(1R,2R)-1-(4-(Methylthio)phenyl)-2-nitropropane-1,3-diol (**7k**).* Pale yellow oil, 96 h, 228.7 mg, 94% yield, *syn*/*anti* = 89:11; ^{1}H NMR (400 MHz, CD_3OD): δ 7.35−7.23 (m, 4H), 5.01 (d, J = 7.2 Hz, 1H, *anti*), 4.96 (d, J = 9.6 Hz, 1H, *syn*), 4.84−4.78 (m, 1H), 4.20 (dd, J_1 = 12.0 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.03 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *anti*), 3.83 (dd, J_1 = 12.0 Hz, J_2 = 9.2 Hz, 1H, *syn*), 3.39 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *syn*), 2.48 (s, 3H, *syn*), 2.46 (s, 3H, *anti*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 139.7 (*syn*), 139.1 (*anti*), 136.4 (*anti*), 136.1 (*syn*), 127.1 (*syn*), 126.8 (*anti*), 126.1 (*syn*), 125.9 (*anti*), 95.2 (*syn*), 94.4 (*anti*), 72.0 (*anti*), 71.9 (*syn*), 60.5 (*syn*), 60.1 (*anti*), 14.1 (*anti*), 14.0 (*syn*) ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_4S$+Na 266.0463, found 266.0465; $[\alpha]_D^{25}$ = −22.8 (c = 0.64, EtOH). The enantiomeric excess of product **7k** was determined by chiral HPLC: 98% ee (CHIRALPAK IC, hexane/*i*-PrOH = 85/15, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 10.238 min, t_{minor} = 12.527 min; *syn* isomer: t_{major} = 17.665 min, t_{minor} = 20.517 min.

*(1R,2R)-1-([1,1′-Biphenyl]-4-yl)-2-nitropropane-1,3-diol (**7l**).* White solid, mp 122−126 °C, 96 h, 259.6 mg, 95% yield, *syn*/*anti* = 93:7; ^{1}H NMR (400 MHz, CD_3OD): δ 7.58−7.49 (m, 4H), 7.38 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.26−7.21 (m, 1H), 4.95 (d, J = 9.2 Hz, 1H), 4.80−4.75 (m, 1H), 3.78 (dd, J_1 = 12.0 Hz, J_2 = 9.2 Hz, 1H), 3.34 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 141.5, 140.3, 138.6, 128.5, 127.2, 127.1, 127.0, 126.6, 95.2, 72.1, 60.5 ppm. ESI HRMS: calcd. for $C_{15}H_{15}NO_4$+Na 296.0899, found 296.0894; $[\alpha]_D^{25}$ = −24.3 (c = 0.68, EtOH). The enantiomeric excess of product **7l** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 85/15, flow rate: 0.8 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 12.060 min, t_{minor} = 14.489 min; *syn* isomer: t_{major} = 20.987 min, t_{minor} = 23.151 min.

*4-((1R,2R)-1,3-Dihydroxy-2-nitropropyl)phenyl acetate (**7m**).* Colorless oil, 132 h, 194.0 mg, 76% yield, *syn*/*anti* = 94:6; ^{1}H NMR (400 MHz, CD_3OD): δ 7.46−7.44 (m, 2H), 7.15−7.13 (m, 2H), 5.04 (d, J = 9.2 Hz, 1H), 4.84 (td, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.85 (dd, J_1 = 12.4 Hz, J_2 = 9.6 Hz, 1H), 3.42 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H), 2.27 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 171.0, 152.1, 138.2, 128.8, 122.9, 96.2, 72.7, 61.5, 20.7 ppm. ESI HRMS: calcd. for $C_{11}H_{13}NO_6$ + Na 278.0641, found 278.0640; $[\alpha]_D^{25}$ = −17.6 (c = 0.78, EtOH). The enantiomeric excess of product **7m** was determined by chiral HPLC: 98% ee (CHIRALPAK IC, hexane/*i*-PrOH = 85/15, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 15.340 min, t_{minor} = 17.904 min; *syn* isomer: t_{major} = 24.200 min, t_{minor} = 28.347 min.

*(1R,2R)-1-(2-Fluorophenyl)-2-nitropropane-1,3-diol (**7n**).* Colorless oil, 72 h, 210.9 mg, 98% yield, *syn*/*anti* = 96:4; ^{1}H NMR (400 MHz, CD_3OD): δ 7.55 (td, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.43−7.37 (m, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.17−7.13 (m, 1H), 5.36 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 4.96−4.93 (m, 1H), 3.96 (td, J_1 = 12 Hz, J_2 = 2.8 Hz, 1H), 3.96 (dt, J_1 = 12 Hz, J_2 = 3.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 160.9 (d, J = 244.0 Hz, *syn*), 160.9 (d, J = 244.1 Hz, *anti*), 131.3 (d, J = 8.5 Hz, *syn*), 131.0 (d, J = 7.7 Hz, *anti*), 129.3 (d, J = 3.9 Hz, *syn*), 129.2 (d, J = 3.8 Hz, *anti*), 127.6 (d, J = 13.2 Hz), 125.6 (d, J = 3.4 Hz, *syn*), 125.2 (d, J = 3.4 Hz, *anti*), 116.1 (d, J = 21.4 Hz, *syn*), 116.0 (d, J = 21.7 Hz, *anti*), 95.6 (d, J = 2.5 Hz, *syn*), 93.5 (*anti*), 67.6 (*anti*), 66.9 (*syn*), 61.2 (*syn*), 40.4 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{10}FNO_4$+Na 238.0492, found 238.0487; $[\alpha]_D^{25}$ = −12.0 (c = 0.52, EtOH). The enantiomeric excess of product **7n** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 12.327 min, t_{minor} = 15.067 min; *syn* isomer: t_{major} = 16.038 min, t_{minor} = 20.773 min.

*(1R,2R)-1-(2-Chlorophenyl)-2-nitropropane-1,3-diol (**7o**).* Pale yellow oil, 108 h, 222.3 mg, 96% yield, *syn*/*anti* = 92:8; ^{1}H NMR (400 MHz, CD_3OD): δ 7.63 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.47−7.34 (m, 3H), 5.57 (d, J = 8.4 Hz, 1H), 4.99−4.94 (m, 1H), 4.14 (dd, J_1 = 12.0 Hz, J_2 = 9.6 Hz, 1H), 3.51 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 138.2, 133.1, 130.6, 130.2, 129.2, 128.4, 96.0, 69.0, 61.1 ppm. ESI HRMS: calcd. for $C_9H_{10}ClNO_4$+Na 254.0196, found 254.0193; $[\alpha]_D^{25}$ = −11.4 (c = 1.15, EtOH). The enantiomeric excess of product **7o** was determined by chiral HPLC: 97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 15.711 min, t_{minor} = 14.266 min; *syn* isomer: t_{major} = 17.139 min, t_{minor} = 21.539 min.

*(1R,2R)-1-(2-Bromophenyl)-2-nitropropane-1,3-diol (**7p**).* White solid, mp 70−73 °C, 108 h, 270.6 mg, 98% yield, *syn*/*anti* = 92:8; ^{1}H NMR (400 MHz, CD_3OD): δ 7.61 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.57 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 7.43 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.25 (td, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 5.49 (d, J = 8.4 Hz, 1H), 4.92−4.89 (m, 1H), 4.15−4.09 (m 1H), 3.43 (dd, J_1 = 12 Hz, J_2 = 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 139.0, 132.6, 129.9, 128.5, 127.9, 122.1, 95.3, 70.4, 60.2 ppm. ESI HRMS: calcd. for $C_9H_{10}BrNO_4$+Na 297.9691, found 297.9689; $[\alpha]_D^{25}$ = −3.3 (c = 0.33, EtOH). The enantiomeric excess of product **7p** was determined by chiral HPLC: 96% ee (CHIRALPAK IC, hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 44.035 min, t_{minor} = 37.405 min; *syn* isomer: t_{major} = 48.952 min, t_{minor} = 65.461 min.

*(1R,2R)-2-Nitro-1-(o-tolyl)propane-1,3-diol (**7q**).* Colorless oil, 132 h, 171.1 mg, 81% yield, *syn*/*anti* = 91:9; ^{1}H NMR (400 MHz, CD_3OD): δ 7.48−7.45 (m, 1H, *anti*), 7.42−7.40 (m, 1H, *syn*), 7.27−7.14 (m, 3H), 5.34 (d, J = 6.8 Hz, 1H, *anti*), 5.29 (d, J = 9.6 Hz, 1H, *syn*), 4.93 (td, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H, *syn*), 4.28 (dd, J_1 = 12.8 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.02 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.85 (dd, J_1 = 12.0 Hz, J_2 = 9.6 Hz, 1H, *syn*), 3.35 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H, *syn*), 2.42 (s, 3H, *syn*), 2.40 (s, 3H, *anti*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 138.9 (*anti*), 138.6 (*syn*), 136.6 (*syn*), 136.3 (*anti*), 131.6 (*syn*), 131.4 (*anti*), 129.2 (*syn*), 129.0 (*anti*), 127.6 (*syn*), 127.4 (*syn*), 127.2 (*anti*), 127.0 (*anti*), 96.7 (*syn*), 93.9 (*anti*), 70.1 (*anti*), 69.6 (*syn*), 61.4 (*syn*), 60.8 (*anti*), 19.2 (*syn*), 18.8 (*anti*) ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_4$+Na 234.0742, found 234.0733; $[\alpha]_D^{25}$ = −4.3 (c = 1.62, EtOH). The enantiomeric excess of product **7q** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 15.559 min, t_{minor} = 14.526 min; *syn* isomer: t_{major} = 18.721 min, t_{minor} = 24.451 min.

*(1R,2R)-1-(3-Chlorophenyl)-2-nitropropane-1,3-diol (**7r**).* Colorless oil, 72 h, 224.7 mg, 97% yield, *syn*/*anti* = 95:5; ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (s, 1H), 7.40−7.34 (m, 3H), 5.10−5.08 (m, 1H, *anti*), 5.05 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, *syn*), 4.84−4.80 (m, 1H), 4.22 (td,

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H, *anti*), 4.07−4.01 (m, 1H, *anti*), 3.87 (td, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H, *syn*), 3.47 (td, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 142.2 (*anti*), 142.0 (*syn*), 134.3 (*syn*), 134.1 (*anti*), 130.0 (*syn*), 129.7 (*anti*), 128.5 (*syn*), 128.1 (*anti*), 126.6 (*syn*), 126.3 (*anti*), 125.0 (*syn*), 124.7 (*anti*), 94.8 (*syn*), 94.1 (*anti*), 71.5 (*anti*), 71.5 (*syn*), 60.4 (*syn*), 59.9 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{10}ClNO_4$+Na 254.0196, found 254.0195; $[\alpha]_D^{25}$ = −12.1 (*c* = 1.86, EtOH). The enantiomeric excess of product **7r** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 25.832 min, t_{minor} = 30.432 min; *syn* isomer: t_{major} = 46.861 min, t_{minor} = 53.726 min.

*(1R,2R)-1-(3-Bromophenyl)-2-nitropropane-1,3-diol (**7s**).* Pale yellow oil, 84 h, 270.6 mg, 98% yield, *syn*/*anti* = 95:5; ^1H NMR (400 MHz, CD_3OD): δ 7.60 (t, *J* = 2.0 Hz, 1H), 7.52−7.49 (m, 1H), 7.38 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 5.03 (t, *J* = 7.2 Hz, 1H, *anti*), 5.00 (t, *J* = 9.2 Hz, 1H, *syn*), 4.77 (td, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 4.18 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 3.99 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.83 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *syn*), 3.43 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 142.6 (*anti*), 142.3 (*syn*), 131.4 (*syn*), 131.0 (*anti*), 130.2 (*syn*), 129.9 (*anti*), 129.6 (*syn*), 129.3 (*anti*), 125.5 (*syn*), 125.1 (*anti*), 122.3 (*syn*), 122.0 (*anti*), 94.8 (*syn*), 94.1 (*anti*), 71.5 (*anti*), 71.4 (*syn*), 60.3 (*syn*), 59.8 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_{10}BrNO_4$+Na 297.9691, found 297.9682; $[\alpha]_D^{25}$ = −11.5 (*c* = 1.81, EtOH). The enantiomeric excess of product **7s** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 12.247 min, t_{minor} = 14.420 min; *syn* isomer: t_{major} = 19.082 min, t_{minor} = 23.252 min.

*(1R,2R)-2-Nitro-1-(m-tolyl)propane-1,3-diol (**7t**).* Pale yellow oil, 132 h, 185.9 mg, 88% yield, *syn*/*anti* = 95:5; ^1H NMR (400 MHz, CD_3OD): δ 7.26 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 2.0 Hz, 1H), 7.20−7.11 (m, 2H), 4.99 (d, *J* = 6.8 Hz, 1H, *anti*), 4.92 (d, *J* = 9.2 Hz, 1H, *syn*), 4.82−4.76 (m, 1H), 4.19 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.00 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.81 (dd, J_1 = 12.4 Hz, J_2 = 9.6 Hz, 1H, *syn*), 3.33 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H, *syn*), 2.35 (s, 3H, *syn*), 2.33 (s, 3H, *anti*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 140.8 (*anti*), 140.6 (*syn*), 139.5 (*syn*), 139.0 (*anti*), 130.2 (*syn*), 129.7 (*anti*), 129.4 (*syn*), 129.1 (*anti*), 128.2 (*syn*), 127.8 (*anti*), 124.7 (*syn*), 124.3 (*anti*), 96.4 (*syn*), 95.5 (*anti*), 73.5, 61.6 (*syn*), 61.0 (*anti*), 21.1 (*anti*), 21.1 (*syn*) ppm. ESI HRMS: calcd. for $C_{10}H_{13}NO_4$+Na 234.0742, found 234.0733; $[\alpha]_D^{25}$ = −7.4 (*c* = 0.75, EtOH). The enantiomeric excess of product **7t** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 13.748 min, t_{minor} = 17.288 min; *syn* isomer: t_{major} = 21.381 min, t_{minor} = 26.903 min.

*(1R,2R)-1-(3,4-Dichlorophenyl)-2-nitropropane-1,3-diol (**7u**).* Colorless oil, 96 h, 255.5 mg, 96% yield, *syn*/*anti* = 91:9; ^1H NMR (400 MHz, CD_3OD): δ 7.63 (d, *J* = 2.0 Hz, 1H, *syn*), 7.56 (d, *J* = 8.4 Hz, 1H, *syn*), 7.52 (d, *J* = 8.4 Hz, 1H, *anti*), 7.37 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, *syn*), 7.32 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, *anti*), 5.07 (d, *J* = 8.8 Hz, 1H), 4.80 (td, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H), 4.20 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.02 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.87 (dd, J_1 = 12.4 Hz, J_{22} = 9.2 Hz, 1H, *syn*), 3.51 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H, *syn*) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 140.8 (*anti*), 140.6 (*syn*), 132.3 (*syn*), 132.0 (*syn*), 131.8 (*anti*), 130.5 (*syn*), 130.2 (*anti*), 128.7 (*syn*), 128.4 (*anti*), 126.4 (*syn*), 126.1 (*anti*), 94.5 (*syn*), 94.0 (*anti*), 70.9 (*anti*), 70.8 (*syn*), 60.3 (*syn*), 59.8 (*anti*) ppm. ESI HRMS: calcd. for $C_9H_9Cl_2NO_4$+Na 287.9806, found 287.9808; $[\alpha]_D^{25}$ = −22.9 (*c* = 1.75, EtOH). The enantiomeric excess of product **7u** was determined by chiral HPLC: 97% ee (CHIRALPAK AS-H, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 30.273 min, t_{minor} = 19.975 min; *syn* isomer: t_{major} = 27.313 min, t_{minor} = 41.672 min.

*(1R,2R)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitropropane-1,3-diol (**7v**).* Yellow oil, 132 h, 197.8 mg, 82% yield, *syn*/*anti* = 82:18; ^1H NMR (400 MHz, CD_3OD): δ 6.91 (d, *J* = 1.6 Hz, 1H), 6.89−6.76 (m, 2H), 5.95 (s, 2H, *syn*), 5.94 (s, 2H, *anti*), 4.90 (d, *J* = 9.2 Hz, 1H), 4.79−4.73 (m, 1H), 4.17 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *anti*), 4.04 (dd, J_1 = 12.8 Hz, J_2 = 3.2 Hz, 1H, *anti*), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 9.6 Hz, 1H, *syn*), 3.38 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H, *syn*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 148.2 (*syn*), 148.0 (*syn*), 147.8 (*anti*), 147.7 (*anti*), 133.7 (*anti*), 133.4 (*syn*), 120.3 (*syn*), 120.0 (*anti*), 107.8 (*syn*), 107.5 (*anti*), 106.4 (*syn*), 106.3 (*anti*), 101.2 (*syn*), 101.1 (*anti*), 95.3 (*syn*), 94.5 (*anti*), 72.1, 60.5 (*syn*), 60.2 (*anti*) ppm. ESI HRMS: calcd. for $C_{10}H_{11}NO_6$+Na 264.0484, found 264.0477; $[\alpha]_D^{25}$ = −6.3 (*c* = 0.49, EtOH). The enantiomeric excess of product **7v** was determined by chiral HPLC: 95% ee (CHIRALPAK IC, hexane/*i*-PrOH = 80/20, flow rate: 0.8 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 10.609 min, t_{minor} = 14.754 min; *syn* isomer: t_{major} = 17.166 min, t_{minor} = 18.520 min.

*(1R,2R)-1-(2,3-Dimethoxyphenyl)-2-nitropropane-1,3-diol (**7w**).* Colorless oil, 84 h, 239.2 mg, 93% yield, *syn*/*anti* = 93:7; ^1H NMR (400 MHz, CD_3OD): δ 7.12(t, *J* = 8.0 Hz, 1H), 7.05−6.99 (m, 2H), 5.34 (dd, J_1 = 9.2 Hz, J_2 = 1.6 Hz, 1H), 4.93−4.88 (m, 1H), 3.96−3.92 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.36 (dt, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 153.7 (*syn*), 153.6 (*anti*), 147.5 (*syn*), 147.2 (*anti*), 134.0 (*anti*), 133.9 (*syn*), 125.5 (*syn*), 124.9 (*anti*), 119.9 (*syn*), 119.8 (*anti*), 113.7 (*syn*), 113.6 (*anti*), 96.4 (*syn*), 93.8 (*anti*), 69.1 (*anti*), 67.8 (*syn*), 61.7 (*syn*), 61.1 (*syn*), 60.9 (*anti*), 60.2 (*anti*), 56.0 (*syn*) ppm. ESI HRMS: calcd. for $C_{11}H_{15}NO_6$+Na 280.0797, found 280.0800; $[\alpha]_D^{25}$ = 8.0 (*c* = 1.13, EtOH). The enantiomeric excess of product **7w** was determined by chiral HPLC: 99% ee (CHIRALPAK IC, hexane/*i*-PrOH = 80/20, flow rate: 0.8 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 15.954 min, t_{minor} = 14.887 min; *syn* isomer: t_{major} = 17.856 min, t_{minor} = 18.930 min.

*(1R,2R)-2-Nitro-1-(2,4,6-trimethoxyphenyl)propane-1,3-diol (**7x**).* White solid, mp 160−163 °C, 84 h, 281.6 mg, 98% yield, *syn*/*anti* = 99:1; ^1H NMR (400 MHz, CD_3OD): δ 6.27 (s, 2H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.38 (td, J_1 = 10.4 Hz, J_2 = 3.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82−3.79 (m, 1H), 3.34−3.32 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 162.2, 159.2, 106.1, 94.2, 90.6, 64.6, 60.7, 54.9, 54.5 ppm. ESI HRMS: calcd. for $C_{12}H_{17}NO_7$+Na 310.0903, found 310.0910; $[\alpha]_D^{25}$ = 15.4 (c = 0.63, EtOH). The enantiomeric excess of product **7x** was determined by chiral HPLC: >99% ee (CHIRALPAK AD-H, hexane/*i*-PrOH = 70/30, flow rate: 0.7 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 10.902 min, t_{minor} = 12.330 min; *syn* isomer: t_{major} = 15.695 min, t_{minor} = 12.979 min.

*(1R,2R)-1-(Naphthalen-2-yl)-2-nitropropane-1,3-diol (**7y**).* Pale yellow oil, 132 h, 202.8 mg, 82% yield, *syn*/*anti* = 89:11; ^1H NMR (400 MHz, CD_3OD): δ 7.90−7.81 (m, 4H), 7.55−7.45 (m, 3H), 5.24 (dd, J_1 = 7.2 Hz, J_2 = 3.2 Hz, 1H, *anti*), 5.18 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H, *syn*), 4.99−4.94 (m, 1H), 4.31−4.25 (m, 1H, *anti*), 4.10−4.05 (m, 1H, *anti*), 3.89 (td, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1H, *syn*), 3.38 (dt, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H, *syn*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 137.3 (*anti*), 137.0 (*syn*), 133.6 (*syn*), 133.5 (*anti*), 133.4 (*syn*), 133.2 (*anti*), 128.5 (*syn*), 128.1 (*anti*), 127.8 (*syn*), 127.5 (*syn*), 127.4, 126.3 (*syn*), 126.2 (*syn*), 126.1 (*anti*), 126.1 (*anti*), 125.6 (*anti*), 123.8 (*syn*), 123.7 (*anti*), 95.3 (*syn*), 94.4 (*anti*), 72.7 (*anti*), 72.6 (*syn*), 60.7 (*syn*), 60.1 (*anti*) ppm. ESI HRMS: calcd. for $C_{13}H_{13}NO_4$+Na 270.0742, found 270.0737; $[\alpha]_D^{25}$ = −10.8 (*c* = 0.68, EtOH). The enantiomeric excess of product **7y** was determined by chiral HPLC: 98% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, *T* = 30 °C, 220 nm), *anti* isomer: t_{major} = 16.384 min, t_{minor} = 21.644 min; *syn* isomer: t_{major} = 28.505 min, t_{minor} = 32.894 min.

*(1S,2R)-1-(Benzofuran-2-yl)-2-nitropropane-1,3-diol (**7z**).* Yellow oil, 60 h, 232.5 mg, 98% yield, *syn*/*anti* = 90:10; ^1H NMR (400 MHz, CD_3OD): δ 7.58 (d, *J* = 7.6 Hz, 1H, *syn*), 7.54 (d, *J* = 7.6 Hz, 1H, *anti*), 7.48 (d, *J* = 8.4 Hz, 1H, *syn*), 7.45 (d, *J* = 8.0 Hz, 1H, *anti*), 7.29 (td, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 7.25−7.18 (m, 1H), 6.86 (s, 1H, *syn*), 6.79 (s, 1H, *anti*), 5.31 (d, *J* = 6.8 Hz, 1H, *anti*), 5.23 (d, *J* = 9.2 Hz, 1H, *syn*), 5.16−5.08 (m, 1H), 4.30 (dd, J_1 = 12.4 Hz, J_2 = 8.8 Hz, 1H, *anti*), 4.11 (dd, J_1 = 12.4 Hz, J_2 = 1.6 Hz, 1H, *anti*), 3.94 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, *syn*), 3.60 (dd, J_1 = 12.4 Hz, J_2 = 3.6 Hz, 1H, *syn*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 156.1 (*anti*), 156.0 (*syn*), 155.9 (*anti*), 155.2 (*syn*), 128.7 (*anti*), 128.6 (*syn*), 125.6 (*syn*), 125.4 (*anti*), 123.8 (*syn*), 123.7 (*anti*), 122.1 (*syn*), 121.9 (*anti*), 111.8 (*syn*), 111.7 (*anti*), 106.3 (*syn*), 105.3 (*anti*), 93.7 (*syn*), 92.4 (*anti*), 67.5 (*anti*), 66.8 (*syn*), 61.3 (*syn*), 60.8 (*anti*) ppm. ESI HRMS: calcd. for $C_{11}H_{11}NO_5$+Na 260.0535, found 260.0532; $[\alpha]_D^{25}$ = −39.9 (*c* = 1.0, EtOH). The enantiomeric excess of product **7z** was determined by chiral HPLC:

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 11.790 min, t_{minor} = 31.974 min; *syn* isomer: t_{major} = 20.296 min, t_{minor} = 24.369 min.

*(1R,2R)-1-(Benzo[b]thiophen-3-yl)-2-nitropropane-1,3-diol (**7aa**).* Yellow oil, 96 h, 233.0 mg, 92% yield, *syn*/*anti* = 95:5; ^{1}H NMR (400 MHz, CD_3OD): δ 8.05 (d, J = 7.6 Hz, 1H, *syn*), 7.98 (d, J = 8.0 Hz, 1H, *anti*), 7.91−7.87 (m, 1H), 7.65 (s, 1H, *syn*), 7.59 (s, 1H, *anti*), 7.44−7.36 (m, 2H), 5.54 (d, J = 6.4 Hz, 1H, *anti*), 5.45 (d, J = 9.2 Hz, 1H, *syn*), 5.21−5.14 (m, 1H, *syn*), 5.12−5.07 (m, 1H, *anti*), 4.33 (dd, J_1 = 12.8 Hz, J_2 = 9.6 Hz, 1H, *anti*), 4.07 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H, *anti*), 3.92 (dd, J_1 = 12.4 Hz, J_2 = 9.6 Hz, 1H, *syn*), 3.41 (dd, J_1 = 12.4 Hz, J_2 = 3.6 Hz, 1H, *syn*) ppm; ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 141.9 (*syn*), 141.8 (*anti*), 137.9 (*syn*), 137.8 (*anti*), 135.8 (*anti*), 135.5 (*syn*), 126.0, 125.5 (*syn*), 125.4 (*anti*), 125.1 (*syn*), 125.0 (*anti*), 123.6 (*syn*), 123.6 (*anti*), 123.2 (*syn*), 122.7 (*anti*), 95.2 (*syn*), 93.7 (*anti*), 69.4 (*anti*), 68.6 (*syn*), 61.7 (*syn*), 60.8 (*anti*) ppm. ESI HRMS: calcd. for $C_{11}H_{11}NO_4S$+Na 276.0306, found 276.0297; $[\alpha]_D^{25}$ = −7.6 (c = 1.90, EtOH). The enantiomeric excess of product **7aa** was determined by chiral HPLC: 98% ee (CHIRALPAK IC, hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, T = 30 °C, 220 nm), *anti* isomer: t_{major} = 15.083 min, t_{minor} = 15.821 min; *syn* isomer: t_{major} = 21.806 min, t_{minor} = 26.908 min.

Continuous Flow Catalytic Hydrogenation Synthesis of 6a. *(1R,2R)-2-Nitro-1-(4-nitrophenyl)propane-1,3-diol (**7a**).* A solution of $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.0 mmol, 10 mol %) and **L9** (419.6 mg, 1.0 mmol, 10 mol %) in THF (15 mL) was stirred for 1 h at room temperature. Then, 4-nitrobenzaldehyde **8a** (1.51 g, 10.0 mmol, 1 equiv) and 2-nitroethanol **9** (2.88 mL, 40.0 mmol, 4 equiv) were added into the reaction flask at 0 °C. The mixture was stirred for 72 h at 0 °C and then quenched with 1 M HCl (30 mL). The resulting mixture was extracted with ethyl acetate (3 × 60 mL). The organic layer was combined and washed with brine (3 × 50 mL). Then, the organic solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude *syn*-2-nitro-1,3-diol **7a**, which was used in the next step without further purification. The crude product was analyzed by HPLC to determine the ratio of *syn*/*anti* and enantiomeric excess: *syn*/*anti* = 90:10, 95% ee (CHIRALPAK AD-H, hexane/*i*-PrOH = 80/20, flow rate: 0.8 mL/min, T = 30 °C, 210 nm), *anti* isomer: t_{major} = 16.378 min, t_{minor} = 14.816 min; *syn* isomer: t_{major} = 17.846 min, t_{minor} = 28.347 min.

*(1R,2R)-2-Amino-1-(4-aminophenyl)propane-1,3-diol (**6a**).* For the flow hydrogenation reaction, the flow system consists of a gas flow meter, a micromixer, a micropacked bed, and a 15 bar back-pressure valve. The mixture containing the above crude **7a** and methanol (333 mL) was delivered by a plunger pump (flow rate: 0.5 mL/min). H_2 gas from the high-pressure-resistant cylinder was fed via a gas flow meter (flow rate: 0.1 L/min). The liquid phase and gas phase were combined by a T-piece connector, entering a micromixer to control the reaction temperature at 25 °C. Then, the reaction stream was passed through a micropacked bed (2.0 g 10% $Pd(OH)_2/C$, 20.0 g SiO_2, and 5 mL internal volume) with 10.0 min residence time. The reaction stream was then collected in a 500 mL flat-bottomed conical flask and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 3:1) to afford **6a** (1.38 g, 76%, two steps) as a white solid. Mp 135−137 °C. ^{1}H NMR (400 MHz, DMSO): δ 6.95 (d, J = 8.0 Hz, 2H), 6.51 (d, J = 8.0 Hz, 2H), 4.89 (s, 2H), 4.18 (d, J = 6.8 Hz, 1H), 3.39 (s, 4H), 3.22 (dd, J_1 = 10.4 Hz, J_2 = 4.4 Hz, 1H), 3.07 (dd, J_1 = 10.4 Hz, J_2 = 6.4 Hz, 1H), 2.63 (td, J_1 = 6.0 Hz, J_2 = 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 147.8, 131.5, 127.6, 113.8, 73.9, 63.4, 59.5 ppm. ESI HRMS: calcd. for $C_9H_{14}N_2O_2$ + Na 205.0953, found 205.0956.

*N-((1R,2R)-1-(4-Aminophenyl)-1,3-dihydroxypropan-2-yl)-2,2-dichloroacetamide (**5a**).* For the flow amidation reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume), a T-mixer, and a 5 bar back-pressure valve. Diamine **6a** (1.82 g, 10.0 mmol, 1.0 equiv) was dissolved in degassed MeOH (24 mL) and placed in one syringe. The mixture containing methyl dichloroacetate **10a** (5.72 g, 40.0 mmol, 4.0 equiv) and degassed MeOH (6 mL) was placed in another syringe. The diamine **6a** syringe was set to 205.2 μL/min, and the methyl dichloroacetate **10a** syringe was set to 80.8 μL/min. The flow was initiated, and the reaction mixture was heated at 40 °C with a 3.5 min residence time. The reaction stream was collected in a 100 mL flat-bottomed conical flask. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:5) to afford **5a** (2.35 g, 80%) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD): δ 7.14 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 6.28 (s, 1H), 4.83 (s, 1H), 4.01 (q, J = 5.6 Hz, 1H), 3.69 (dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz, 1H), 3.47 (dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 166.3, 147.5, 132.8, 128.0, 116.3, 72.1, 67.4, 61.9, 58.9 ppm. ESI HRMS: calcd. for $C_{11}H_{14}Cl_2N_2O_3$ + Na 315.0279, found 315.0275, 317.0248, 319.2014.

Continuous Flow Synthesis of (−)-Chloramphenicol (1). For the flow oxidation reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume), a T-mixer, and a 5 bar back-pressure valve. **5a** (2.0 g, 6.8 mmol, 1.0 equiv), $NaHCO_3$ (5.72 g, 68.0 mmol, 10.0 equiv), and NaOH (322 mg, 8.0 mmol, 1.18 equiv) were dissolved in degassed H_2O/acetone (120 mL, v/v = 2:1) and placed in one syringe. The mixture containing oxone (10.86 g, 17.7 mmol, 2.6 equiv) and degassed 4 × 10^{-4} M EDTA aqueous (60 mL) was placed in another syringe. The **5a** syringe was set to 429.1 μL/min and the oxone syringe was set to 237.5 μL/min. The flow was initiated with a 1.5 min residence time and cooling down the first half of the flow reactor to 0 °C, leaving the second half of the flow reactor length to warm up to room temperature. The reaction stream was collected in a 250 mL flat-bottomed conical flask and quenched with sodium bisulfite. The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The organic layer was combined and washed with brine (100 mL). Then, the organic solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 10:1) to afford (−)-chloramphenicol (**1**) (1.58 g, 72%) as a white solid. The product was subsequently recrystallized from AcOEt/PE, affording (−)-chloramphenicol (**1**) (1.37 g, 62%). Mp = 150−151 °C; $[\alpha]_D^{25}$ = −24.1 (c = 1.0, AcOEt); ^{1}H NMR (400 MHz, DMSO): δ 8.33 (d, J = 9.2 Hz, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 6.48 (s, 1H), 6.05 (d, J = 4.4 Hz, 1H), 5.07 (dd, J_1 = 4.8 Hz, J_2 = 2.4 Hz, 1H), 5.00 (dd, J_1 = 6.0 Hz, J_2 = 4.8 Hz, 1H), 3.98−3.91 (m, 1H), 3.63−3.57 (m, 1H), 3.40−3.37 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 163.9, 151.7, 146.9, 127.8, 123.3, 69.4, 66.9, 60.7, 57.3 ppm. ESI HRMS: calcd. for $C_{11}H_{12}Cl_2N_2O_5$ + Na 345.0021, found 345.0010.

*N-((1R,2R)-1-(4-Aminophenyl)-1,3-dihydroxypropan-2-yl)-2-azidoacetamide (**5b**).* **5b** was prepared from **10b** in 81% yield by the same procedure of **5a**. Yellow oil. ^{1}H NMR (400 MHz, CD_3OD): δ 7.02 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 5.2 Hz, 1H), 3.96 (q, J = 6.0 Hz, 1H), 3.77 (s, 2H), 3.53 (dd, J_1 =11.2 Hz, J_2 = 5.6 Hz, 1H), 3.34 (dd, J_1 = 11.2 Hz, J_2 = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 168.8, 146.8, 131.4, 126.9, 115.0, 71.5, 61.1, 57.2, 51.6 ppm. ESI HRMS: calcd. for $C_{11}H_{15}N_5O_3$ + Na 288.1073, found 288.1069.

Continuous Flow Synthesis of (−)-Azidamphenicol (2). (−)-Azidamphenicol (**2**) was prepared from **5b** in 75% yield by the same procedure of (−)-chloramphenicol (**1**). The product was subsequently recrystallized from AcOEt/PE, affording (−)-azidamphenicol (**2**) in 64% yield. White solid. Mp = 108−109 °C; $[\alpha]_D^{25}$ = −9.8 (c = 1.0, EtOH); ^{1}H NMR (400 MHz, DMSO): δ 8.17 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 9.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 5.92 (d, J = 4.4 Hz, 1H), 5.04 (dd, J_1 = 4.4 Hz, J_2 = 2.4 Hz, 1H), 4.92 (dd, J_1 = 6.4 Hz, J_2 = 4.8 Hz, 1H), 4.03−3.97 (m, 1H), 3.71 (d, J = 2.4 Hz, 2H), 3.59−3.53 (m, 1H), 3.37−3.32 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 167.6, 152.1, 146.8, 127.7, 123.3, 69.7, 60.9, 56.7, 50.9 ppm. ESI HRMS: calcd. for $C_{11}H_{13}N_5O_5$ + Na 318.0814, found 318.0808.

Continuous Flow Catalytic Hydrogenation Synthesis of 6b. *(1R,2R)-1-(4-(Methylsulfonyl)phenyl)-2-nitropropane-1,3-diol (**7b**).* A solution of $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.0 mmol, 10 mol %) and **L9** (419.6 mg, 1.0 mmol, 10 mol %) in THF (15 mL) was stirred for 1 h at room temperature. Then, 4-methylsulfonyl benzaldehyde **8b** (1.84 g, 10.0 mmol, 1 equiv) and 2-nitroethanol **9** (2.88 mL, 40.0 mmol, 4 equiv) were added into the reaction flask at 0 °C. The mixture was stirred for 72 h at 0 °C, then quenched with 1 M HCl (30 mL). The resulting mixture was extracted with ethyl acetate (3 × 60 mL). The

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

organic layer was combined and washed with brine (3 × 50 mL). Then, the organic solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude *syn*-2-nitro-1,3-diol **7b**, which was used in the next step without further purification. The crude product was analyzed by HPLC to determine the ratio of *syn*/*anti* and enantiomeric excess: *syn*/*anti* = 95:5, 97% ee (CHIRALPAK IC, hexane/*i*-PrOH = 65/35, flow rate: 0.7 mL/min, T = 30 °C, 210 nm).

*(1R,2R)-2-Amino-1-(4-(methylsulfonyl)phenyl)propane-1,3-diol (**6b**).* For the flow hydrogenation reaction, the flow system consists of a gas flow meter, a micromixer, a micropacked bed, and a 15 bar back-pressure valve. The mixture containing the above crude **7b** and methanol (333 mL) was delivered by a plunger pump (flow rate: 0.5 mL/min). H_2 gas from the high-pressure-resistant cylinder was fed via a gas flow meter (flow rate: 0.1 L/min). The liquid phase and gas phase were combined by a T-piece connector, entering a micromixer to control the reaction temperature at 25 °C. Then, the reaction stream was passed through a micropacked bed (2.0 g 10% $Pd(OH)_2/C$, 20.0 g SiO_2, and 5 mL internal volume) with 10.0 min residence time. The reaction stream was then collected in a 500 mL flat-bottomed conical flask and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 3:1) to afford **6b** (2.01 g, 82%, two steps) as a white solid. Mp = 142−143 °C; $[\alpha]_D^{25}$ = −22.4 (c = 0.28, EtOH); ^{1}H NMR (400 MHz, CD_3OD): δ 7.93 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 4.76 (d, J = 5.6 Hz, 1H), 3.53 (dd, J_1 = 10.8 Hz, J_2 = 5.2 Hz, 1H), 3.39 (dd, J_1 = 10.8 Hz, J_2 = 6.0 Hz, 1H), 3.12 (s, 3H), 2.90 (dd, J_1 = 10.8 Hz, J_2 = 5.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 150.8, 140.7, 128.4, 128.1, 74.0, 63.8, 59.5, 44.2 ppm. ESI HRMS: calcd. for $C_{10}H_{15}NO_4S$ + Na 268.0619, found 268.0614.

Continuous Flow Synthesis of (+)-Thiamphenicol (3). For the flow amidation reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume) and a T-mixer. *syn*-2-Amino-1,3-diol **6b** (1.23 g, 5.0 mmol, 1.0 equiv) was dissolved in degassed MeOH (14 mL) and placed in one syringe. The mixture containing methyl dichloroacetate **10a** (2.15 g, 15.0 mmol, 3.0 equiv), Et_3N (1.0 g, 10.0 mmol, 2.0 equiv), and degassed MeOH (3 mL) was placed in another syringe. The *syn*-2-amino-1,3-diol **6b** syringe was set to 77.6 μL/min and the methyl dichloroacetate **10a** syringe was set to 22.4 μL/min. The flow was initiated, and the reaction mixture was heated at 30 °C with a 10.0 min residence time. The reaction stream was collected in a 100 mL flat-bottomed conical flask. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:10) to afford (+)-thiamphenicol (**3**) (1.71 g, 96%) as a white solid. The product was subsequently recrystallized from MeOH/PE, affording (+)-thiamphenicol (**3**) (1.50 g, 84%). Mp 164−165 °C; $[\alpha]_D^{20}$ = +12.6 (c = 1.0, EtOH); ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 6.25 (s, 1H), 5.16 (d, J = 2.8 Hz, 1H), 4.15 (td, J_1 = 6.4 Hz, J_2 = 2.8 Hz, 1H), 3.83 (dd, J_1 = 10.8 Hz, J_2 = 6.8 Hz, 1H), 3.62 (dd, J_1 = 10.8 Hz, J_2 = 6.0 Hz, 1H), 3.10 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): δ 165.1, 149.0, 139.4, 126.9, 126.8, 70.0, 66.0, 60.8, 57.1, 43.0 ppm. ESI HRMS: calcd. for $C_{12}H_{15}Cl_2NO_5S$ + Na 377.9946, found 377.9941.

*((4R,5R)-2-(Dichloromethyl)-5-(4-(methylsulfonyl)phenyl)-4,5-dihydrooxazol-4-yl)methanol (**11**).* For the flow cyclization reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume), a T-mixer, and a 10 bar back-pressure valve. *syn*-2-Amino-1,3-diol **6b** (1.23 g, 5.0 mmol, 1.0 equiv) was dissolved in degassed MeOH (6 mL) and placed in one syringe. The mixture containing dichloroacetonitrile (616 mg, 5.6 mmol, 1.12 equiv), conc. HCl (126 μL), and degassed MeOH (1 mL) was placed in another syringe. The *syn*-2-amino-1,3-diol **6b** syringe was set to 80.6 μL/min and the dichloroacetonitrile syringe was set to 19.4 μL/min. The flow was initiated, and the reaction mixture was heated at 70 °C with a 10.0 min residence time. The reaction stream was collected in a 100 mL flat-bottomed conical flask. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (DCM/MeOH = 100:10) to afford **11** (1.49 g, 88%) as a white solid. Mp 144−145 °C; $[\alpha]_D^{20}$ = +11.2 (c = 1.0, EtOH); ^{1}H NMR (400 MHz, DMSO): δ 7.99 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 5.75 (d, J = 6.4 Hz, 1H), 5.17 (t, J = 5.6 Hz, 1H), 4.08 (dd, J_1 = 10.8 Hz, J_2 = 5.6 Hz, 1H), 3.75−3.70 (m, 1H), 3.60−3.55 (m, 1H), 3.23 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 161.3, 146.4, 141.0, 128.1, 126.5, 83.3, 76.9, 62.4, 43.9 ppm. ESI HRMS: calcd. for $C_{12}H_{13}Cl_2NO_4S$ + Na 359.9840, found 359.9843.

Continuous Flow Synthesis of (+)-Florfenicol (4). *(4S,5R)-2-(Dichloromethyl)-4-(fluoromethyl)-5-(4-(methylsulfonyl)phenyl)-4,5-dihydrooxazole (**12**).* For the flow fluorination reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume) and a 10 bar back-pressure valve. Oxazoline **11** (3.38 g, 10.0 mmol, 1.0 equiv) was dissolved in dry DCM (50 mL) and placed in one syringe. The oxazoline **11** syringe was set to 400 μL/min. The flow was initiated, and the reaction mixture was heated at 100 °C with a 2.5 min residence time. The reaction stream was collected in a 100 mL flat-bottomed conical flask. After collection of the organic reaction solution, the solvent was removed in vacuo to afford product **12**, which was used in the next stage without the need for further purification. White solid. Mp 123−126 °C. $[\alpha]_D^{25}$ = −12.2 (c = 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 6.35 (s, 1H), 5.72 (d, J = 6.8 Hz, 1H), 4.78−4.53 (m, 2H), 4.35−4.26 (m, 1H), 3.05 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 145.0, 141.0, 128.3, 126.1, 83.2 (d, J = 4.2 Hz), 82.6 (d, J = 173.1 Hz), 74.6 (d, J = 31.9 Hz), 60.9, 44.4 ppm. ESI HRMS: calcd. for $C_{12}H_{12}Cl_2FNO_3S$ + Na 361.9797, found 361.9795.

*(+)-Florfenicol (**4**).* For the flow hydrolysis reaction, the reactor coil consists of a 200 cm segment of a PTFE tube (i.d. = 0.8 mm, 1.0 mL total volume) and a 10 bar back-pressure valve. The above crude **12** was dissolved in ^{i}PrOH/H_2O (40 mL, v/v = 1.86:1) and placed in one syringe. The syringe was set to 400 μL/min. The flow was initiated, and the reaction mixture was heated at 100 °C with a 2.5 min residence time. The reaction stream was collected in a 100 mL flat-bottomed conical flask. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (AcOEt/PE = 1:1) to afford (+)-florfenicol (**4**) (3.26 g, 91%) as a white solid. The product was subsequently recrystallized from AcOEt/PE, affording (+)-florfenicol (**4**) (2.90 g, 81%). Mp 151−152 °C; $[\alpha]_D^{25}$ = −18.8 (c = 1.0, DMF); ^{1}H NMR (400 MHz, DMSO): δ 8.61 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 6.14 (d, J = 4.4 Hz, 1H), 4.98 (t, J = 3.6 Hz, 1H), 4.72−4.57 (m, 1H), 4.58−4.24 (m, 2H), 3.15 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO): δ 164.2, 148.3, 140.0, 127.6, 126.9, 82.8 (d, J = 169.0 Hz), 69.8 (d, J = 6.0 Hz), 66.7, 55.0 (d, J = 19.6 Hz), 44.0 ppm. ESI HRMS: calcd. for $C_{12}H_{14}Cl_2FNO_4S$ + Na 379.9902, found 379.9908.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01124.

Experimental procedures, HPLC data, compound characterization, NMR spectra, and HRMS spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Fener Chen − *Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China; Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China; Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, China;* orcid.org/0000-0002-6734-3388; Email: rfchen@fudan.edu.cn

Authors

Yingqi Xia − *Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX

Meifen Jiang − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China*
Minjie Liu − *Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, China*
Yan Zhang − *Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
Hongmin Qu − *Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
Tong Xiong − *Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
Huashan Huang − *Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, China*
Dang Cheng − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China;* orcid.org/0000-0001-5899-5141

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01124

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Fundamental Research Funds for the Central Universities (YJ201805 and YJ201864).

■ REFERENCES

(1) (a) Cutler, R. A.; Stenger, R. J.; Suter, C. M. New Antibacterial Agents. 2-Acylamino-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediols and Related Compounds. *J. Am. Chem. Soc.* **1952**, *74*, 5475−5478. (b) Suter, C. M.; Schalit, S.; Cutler, R. A. New Antibacterial Agents. II. An Alternate Synthesis of DL-threo-2-Dichloro-acetamido-1-(4-methylsulfonylphenyl)-1, 3-propanediol. *J. Am. Chem. Soc.* **1953**, *75*, 4330−4333. (c) Jommi, G.; Pagliarin, R.; Chiarino, D.; Fantucci, M. 2-Oxazolidinones as regioselective protection of β-amino alcohols in the synthesis of 2-amino-1-aryl-3-fluoro-1-propanols. *Gazz. Chim. Ital.* **1985**, *115*, 653−658. (d) Schumacher, D. P.; Clark, J. E.; Murphy, B. L.; Fischer, P. A. An efficient synthesis of florfenicol. *J. Org. Chem.* **1990**, *55*, 5291−5294. (e) Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. Direct conversion of (1S,2S)-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol into its enantiomer for efficient synthesis of thiamphenicol and florfenicol. *J. Org. Chem.* **1991**, *56*, 6114−6118. (f) Clark, J. E.; Fischer, P. A.; Schumacher, D. P. An Enzymatic Route to Florfenicol. *Synthesis* **1991**, *1991*, 891−894.

(2) (a) Horsberg, T. E.; Hoff, K. A.; Nordmo, R. Pharmacokinetics of Florfenicol and Its Metabolite Florfenicol Amine in Atlantic Salmon. *J. Aquat. Anim. Health* **1996**, *8*, 292−301. (b) Shen, J.; Hu, F.; Wu, X.; Coats, J. R. Bioavailability and pharmacokinetics of florfenicol in broiler chickens. *J. Vet. Pharmacol. Ther.* **2003**, *26*, 337−341. (c) Ueda, Y.; Ohtsuki, S.; Narukawa, N. Efficacy of Florfenicol on Experimental Actinobacillus Pleuropneumonia in Pigs. *J. Vet. Med. Sci.* **1995**, *57*, 261−265. (d) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Joslyn, D. A.; Burkholder, P. R. Chloromycetin, a New Antibiotic From a Soil Actinomycete. *Science* **1947**, *106*, 417. (e) Rebstock, M. C.; Crooks, H. M.; Controulis, J.; Bartz, Q. R. Chloramphenicol (Chloromycetin).1 IV.1a Chemical Studies. *J. Am. Chem. Soc.* **1949**, *71*, 2458−2462.

(3) (a) Madhavan, H. N.; Bagyalakshmi, R. Farewell, Chloramphenicol? Is this True?: A Review. *Res. Rev. J. Microbiol. Biotechnol.* **2014**, *3*, 13−26. (b) Aspa, J.; Rajas, O.; Castro, F. R.; Blanquer, J.; Zalacain, R.; Fenoll, A.; Celis, R.; Vargas, A.; Salvanes, F. R.; Espana, P. P.; Rello, J.; Torres, A. Drug-Resistant Pneumococcal Pneumonia: Clinical Relevance and Related Factors. *Clin. Infect. Dis.* **2004**, *38*, 787−798. (c) Campos, J.; Román, F.; Pérez-Vázquez, M.; Aracil, B.; Oteo, J.; Cercenado, E. Antibiotic resistance and clinical significance of *Haemophilus influenzae* type f. *J. Antimicrob. Chemother.* **2003**, *52*, 961−966. (d) Duke, T. Neonatal pneumonia in developing countries. *Arch. Dis. Child. Fetal Neonatal Ed.* **2005**, *90*, F211−F219. (e) Hartmann, C.; Peter, C.; Hermann, E.; Ure, B.; Sedlacek, L.; Hansen, G.; Bohnhorst, B. Successful treatment of vancomycin-resistant *Enterococcus faecium* ventriculitis with combined intravenous and intraventricular chloramphenicol in a newborn. *J. Med. Microbiol.* **2010**, *59*, 1371−1374. (f) Sood, S.; Kapil, A.; Das, B.; Jain, Y.; Kabra, S. K. Re-emergence of chloramphenicolsensitive *Salmonella typhi*. *Lancet* **1999**, *353*, 1241−1242. (g) Sowmiya, M.; Malathi, J.; Madhavan, H. N. Screening of Ocular Enterobacteriaceae Isolates for Presence of Chromosomal blaNDM-1 and ESBL Genes: A 2-Year Study at a Tertiary Eye Care Center. *Invest. Ophthalmol. Vis. Sci.* **2012**, *53*, 5251−5257. (h) Du, Z.; Wang, M.-Y.; Cui, G.-Y.; Zu, X.-Y.; Zhao, Z.-Q.; Xue, Y. The prevalence of amphenicol resistance in *Escherichia coli* isolated from pigs in mainland China from 2000 to 2018: A systematic review and meta-analysis. *PLoS One* **2020**, *15*, No. e0228388.

(4) Nitzan, O.; Supnitzky, U.; Kennes, Y.; Chazan, B.; Raul, R.; Colodner, R. Is Chloramphenicol Making a Comeback? *Isr. Med. Assoc. J.* **2010**, *12*, 371−374.

(5) (a) Corey, E. J.; Choi, S. Efficient Enantioselective Syntheses of Chloramphenicol and (D)-threo- and (D)-erythro-Sphingosine. *Tetrahedron Lett.* **2000**, *41*, 2765−2768. (b) Hajra, S.; Karmakar, A.; Maji, T.; Medda, A. K. Stereoselective syntheses of (-)-chloramphenicol and (+)-thiamphenicol. *Tetrahedron* **2006**, *62*, 8959−8965. (c) Loncaric, C.; Wulff, W. D. An Efficient Synthesis of (−)-Chloramphenicol via Asymmetric Catalytic Aziridination: A Comparison. *Org. Lett.* **2001**, *3*, 3675−3678. (d) Bhaskar, G.; Kumar, V. S.; Rao, B. V. A Short Stereoselective Synthesis of (-)-Chloramphenicol and (+)-Thiamphenicol. *Tetrahedron: Asymmetry* **2004**, *15*, 1279−1283. (e) Wu, G.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. An Improved Industrial Synthesis of Florfenicol plus an Enantioselective Total Synthesis of Thiamphenicol. *J. Org. Chem.* **1997**, *62*, 2996−2998. (f) Franchino, A.; Jakubec, P.; Dixon, D. J. Enantioselective Synthesis of (−)-Chloramphenicol via Silver-Catalysed Asymmetric Isocyanoacetate Aldol Reaction. *Org. Biomol. Chem.* **2016**, *14*, 93−96. (g) Perez, M.; Echeverria, P. -G.; Martine-Arripe, E.; Zoubir, M. E.; Touati, R.; Zhang, Z.; Genet, J. -P.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. An Efficient Stereoselective Total Synthesis of All Stereoisomers of the Antibiotic Thiamphenicol through Ruthenium-Catalyzed Asymmetric Reduction by Dynamic Kinetic Resolution. *Eur. J. Org. Chem.* **2015**, *2015*, 5949−5958. (h) Zou, J.; Ni, G.; Tang, J.; Yu, J.; Jiang, L.; Ju, D.; Zhang, F.; Chen, S. Asymmetric Synthesis of Florfenicol by Dynamic Reductive Kinetic Resolution with Ketoreductases. *Eur. J. Org. Chem.* **2018**, *2018*, 5044−5053. (i) Lu, W.; Chen, P.; Lin, G. New Stereoselective Synthesis of Thiamphenicol and Florfenicol from Enantiomerically Pure Cyanohydrin: a Chemo-Enzymatic Approach. *Tetrahedron* **2008**, *64*, 7822−7827.

(6) Li, F.; Wang, Z.-H.; Zhao, L.; Chen, F.-E. A Facile and Efficient Asymmetric Synthesis of Florfenicol. *Synlett* **2011**, *19*, 2883−2885.

(7) Li, F.; Wang, Z.-H.; Zhao, L.; Xiong, F.-J.; He, Q.-Q.; Chen, F.-E. An efficient enantioselective synthesis of florfenicol via a vanadium-catalyzed asymmetric epoxidation. *Tetrahedron: Asymmetry* **2011**, *22*, 1337−1341.

(8) Wang, Z.-H.; Zheng, C.; Li, F.; Zhao, L.; Chen, F.-E.; He, Q.-Q. An Efficient Enantioselective Synthesis of Florfenicol Based on Sharpless Asymmetric Dihydroxylation. *Synthesis* **2012**, *44*, 699−704.

(9) Wang, X.-L.; Xu, L.-J.; Yan, L.-J.; Wang, H.-F.; Han, S.; Wu, Y.; Chen, F.-E. Catalytic asymmetric transfer hydrogenation/dynamic kinetic resolution: an efficient synthesis of florfenicol. *Tetrahedron* **2016**, *72*, 1787−1793.

(10) Liu, J.-X.; Li, Y.-L.; Ke, M.-L.; Liu, M.-J.; Zhan, P.-P.; Xiao, Y.-C.; Chen, F.-E. Unified Strategy to Amphenicol Antibiotics: Asymmetric Synthesis of (-)-Chloramphenicol, (-)-Azidamphenicol, and

(+)-Thiamphenicol and Its (+)-3-Floride. *J. Org. Chem.* **2020**, *85*, 15360−15367.
(11) Wang, Z.-H.; Li, F.; Zhao, L.; He, Q.-Q.; Chen, F.-E.; Zheng, C. An efficient enantioselective synthesis of florfenicol via asymmetric aziridination. *Tetrahedron* **2011**, *67*, 9199−9203.
(12) (a) Kim, Y.; Li, C.-J. Perspectives on green synthesis and catalysis. *Green Synth. Catal.* **2020**, *1*, 1−11. (b) Trost, B. M. On Inventing Reactions for Atom Economy. *Acc. Chem. Res.* **2002**, *35*, 695−705. (c) Sheldon, R. A. Metrics of Green Chemistry and Sustainability: Past, Present, and Future. *ACS Sustainable Chem. Eng.* **2018**, *6*, 32−48. (d) Li, L.; Chen, Z.; Zhang, X.-W.; Jia, Y.-X. Divergent Strategy in Natural Product Total Synthesis. *Chem. Rev.* **2018**, *118*, 3752−3832.
(13) (a) Qin, D.-D.; Lai, W.-H.; Hu, D.; Chen, Z.; Wu, A.-A.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. Highly Enantioselective Henry Reactions of Aromatic Aldehydes Catalyzed by an Amino Alcohol−Copper(II) Complex. *Chem. − Eur. J.* **2012**, *18*, 10515−10518. (b) Qin, D.-D.; Yu, W.; Zhou, J.-D.; Zhang, Y.-C.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. syn- and Enantioselective Henry Reactions of Aliphatic Aldehydes and Application to the Synthesis of Safingol. *Chem. − Eur. J.* **2013**, *19*, 16541−16544.
(14) For reviews on the asymmetric Henry reactions: (a) Luzzio, F. A. The Henry reaction: recent examples. *Tetrahedron* **2001**, *57*, 915−945. (b) Palomo, C.; Oiarbide, M.; Mielgo, A. Unveiling Reliable Catalysts for the Asymmetric Nitroaldol (Henry) Reaction. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442−5444. (c) Palomo, C.; Oiarbide, M.; Laso, A. Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 2561−2574. (d) Murugavel, G.; Sadhu, P.; Punniyamurthy, T. Copper(II)-Catalyzed Nitroaldol (Henry) Reactions: Recent Developments. *Chem. Rec.* **2016**, *16*, 1906−1917. (e) Saranya, S.; Harry, N. A. S.; Ujwaldev, M.; Anilkumar, G. Recent Advances and Perspectives on the Zinc-Catalyzed Nitroaldol (Henry) Reaction. *Asian J. Org. Chem.* **2017**, *6*, 1349−1360. (f) Zhang, S.; Li, Y.-N.; Xu, Y.-G.; Wang, Z.-Y. Recent progress in copper catalyzed asymmetric Henry reaction. *Chin. Chem. Lett.* **2018**, *29*, 873−883. (g) Dong, L.; Chen, F.-E. Asymmetric catalysis in direct nitromethane-free Henry reactions. *RSC Adv.* **2020**, *10*, 2313−2326. (h) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. Catalytic asymmetric Henry reaction. *Tetrahedron: Asymmetry* **2006**, *17*, 3315−3326. (i) Marcelli, T.; Haas, R. N. S.; Maarseveen, J. H.; Hiemstra, H. Asymmetric Organocatalytic Henry Reaction. *Angew. Chem., Int. Ed.* **2006**, *45*, 929−931.
(15) (a) Tseng, S.-L.; Yang, T.-K. New β-amino thiols as efficient catalysts for highly enantioselective alkenylzinc addition to aldehydes. *Tetrahedron: Asymmetry* **2005**, *16*, 773−782. (b) Guo, Z.-L.; Zhong, S.; Li, Y.-B.; Lu, G. Chiral 1,1′-binaphthylazepine derived amino alcohol catalyzed asymmetric Henry reaction. *Tetrahedron: Asymmetry* **2011**, *22*, 238−245.
(16) For reviews on flow chemistry: (a) Pastre, J. C.; Browne, D. L.; Ley, S. V. Flow chemistry syntheses of natural products. *Chem. Soc. Rev.* **2013**, *42*, 8849−8869. (b) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhikers Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117*, 11796−11893. (c) Wiles, C.; Watts, P. Recent advances in micro reaction technology. *Chem. Commun.* **2011**, *47*, 6512−6535. (d) Baumann, M.; Baxendale, I. R. The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry. *Beilstein J. Org. Chem.* **2015**, *11*, 1194−1219. (e) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process: Res. Dev.* **2016**, *20*, 2−25. (f) Rogers, L.; Jensen, K. F. Continuous manufacturing - the Green Chemistry promise? *Green Chem.* **2019**, *21*, 3481−3498. (g) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology-A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6728. (h) Jas, G.; Kirschning, A. Continuous Flow Techniques in Organic Synthesis. *Chem. − Eur. J.* **2003**, *9*, 5708−5723. (i) Liao, J.-Y.; Zhang, S.-L.; Wang, Z.-S.; Song, X.; Zhang, D.-L.; Kumar, R.; Jin, J.; Ren, P.; You, H.-Z.; Chen, F.-E. Transition-metal catalyzed asymmetric reactions under continuous flow from 2015 to early 2020. *Green Synth. Catal.* **2020**, *1*, 121−133.
(17) For selected review and example on hydrogenation in continuous-flow: (a) Irfan, M.; Glasnov, T. N.; Kappe, C. O. Heterogeneous Catalytic Hydrogenation Reactions in Continuous-Flow Reactors. *ChemSusChem* **2011**, *4*, 300−316. (b) Newton, S.; Ley, S. V.; Arce, E. C.; Grainger, D. M. Asymmetric Homogeneous Hydrogenation in Flow using a Tube-in-Tube Reactor. *Adv. Synth. Catal.* **2012**, *354*, 1805−1812. (c) Ishitani, H.; Kanai, K.; Yoo, W.-J.; Yoshida, T.; Kobayashi, S. Nickel-Diamine/Mesoporous Silica Composite as a Heterogeneous Chiral Catalyst for Asymmetric 1,4-Addition Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 13313−13317. (d) Yoswathananont, N.; Nitta, K.; Nishiuchi, Y.; Sato, M. Continuous hydrogenation reactions in a tube reactor packed with Pd/C. *Chem. Commun.* **2005**, 40−42. (e) Saaby, S.; Knudsen, K. R.; Ladlowb, M.; Ley, S. V. The use of a continuous flow-reactor employing a mixed hydrogen−liquid flow stream for the efficient reduction of imines to amines. *Chem. Commun.* **2005**, 2909−2911. (f) Yang, C.-X.; Teixeira, A. R.; Shi, Y.-X.; Born, S. C.; Lin, H.-K.; Song, Y. F. L.; Martin, B.; Schenkel, B.; Lachegurabia, M. P.; Jensen, K. F. Catalytic hydrogenation of N-4-nitrophenyl nicotinamide in a micro-packed bed reactor. *Green Chem.* **2018**, *20*, 886−893. (g) Tu, J.-C.; Sang, L.; Cheng, H.; Ai, N.; Zhang, J.-S. Continuous Hydrogenolysis of N-Diphenylmethyl Groups in a Micropacked-Bed Reactor. *Org. Process: Res. Dev.* **2020**, *24*, 59−66.

https://doi.org/10.1021/acs.joc.1c01124
J. Org. Chem. XXXX, XXX, XXX−XXX