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Practical and Scalable Manufacturing Process for the Key Intermediate of Poly(ADP-Ribose) Polymerase Inhibitor Olaparib

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ABSTRACT: Olaparib (Lynparza) is a potent, highly selective inhibitor of poly(ADP-ribose)polymerase enzymes, approved by the U.S. FDA and EMA for the treatment of ovarian cancer. Herein, we report a practical, economical, and scalable process for the synthesis of 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)-methyl)benzoic acid, a key intermediate for olaparib. The low-cost industrial byproduct phthalhydrazide was used as the starting material to construct the phthalazinone moiety, which allowed access to the key intermediate by the Negishi coupling reaction. Optimization of each step has enabled the development of an environmentally benign and robust process with effective control of impurities.
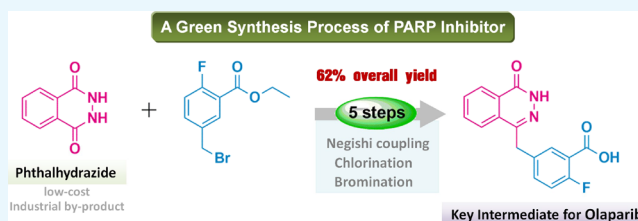
INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) are enzymes involved in DNA repair,[1] which play an important role in DNA damage repair and provide a target for cancer therapy.[2] PARP inhibitors (PARPi) are the first clinically approved drugs designed to exploit synthetic lethality.[3]

Lynparza (olaparib), Rubraca (rucaparib), and Zejula (niraparib) are three PARPi that have been recently approved for the treatment of ovarian cancer (Figure 1). Olaparib is the first-in-class PARPi and the first targeted treatment to potentially exploit DNA damage response pathway deficiencies, such as BRCA (Breast Cancer) mutations, to not only preferentially kill cancer cells but also modulate therapy outcome of treatment with platinum drugs.[4] On December 19, 2014, the FDA approved olaparib capsules (Lynparza; AstraZeneca) for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.[5]

The original medicinal chemistry route for olaparib proceeded in six steps and 46% yield (Scheme 1).[6] First, phosphonate 2 with a yield of 95% was obtained by 2-formylbenzoic acid 1 with dimethylphosphite, and then reacted with aldehyde 3 by the Horner−Wadsworth−Emmons reaction to synthesize olefin 4 ($E:Z = 1:1$) in 96% yield. Compound 4 was hydrolyzed to acid under alkaline conditions, and then reacted with hydrazine hydrate in the same reaction system, affording key intermediate 5 with a total yield of 77%. Compound 6 with a yield of 78% was obtained by the condensation reaction of 5 and N-Boc-piperazine under 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophos-

phate condition. The Boc group was removed in hydrochloric acid, and then reacted with cyclopropane carbonyl chloride to synthesize olaparib in 85% yield.

In subsequent process development, the base, reagent, and solvents were optimized to facilitate telescoping the first two reactions of the medicinal chemistry route, with the overall yield of 34%.[7,8] In addition, Wang et al. described two convergent routes to olaparib employing an elaborated aldehyde fragment, affording overall yields 49 and 29%, respectively. However, these routes still required the use of phthalide (or indandione) to build the key intermediate phthalazinone by hydrazinolysis (Scheme 2). The use of hydrazine hydrate was a concern since hydrazine has been shown to induce cancerous tumor growth in animal studies and was classified as a probable human carcinogen by the U.S. Environmental Protection Agency.[9] Meanwhile, because of hydrazine's high carcinogenicity/toxicity, energy content and wide flammability range,[10] we needed to detect the concentration of hydrazine vapor to prevent explosion in the scale-up experiment. According to the calculation of the level of hydrazine in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M7 guideline,[11] the maximum allowed level of hydrazine was 39 μg/day in oral drugs. The
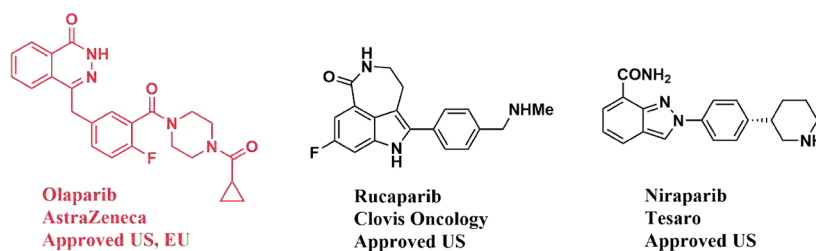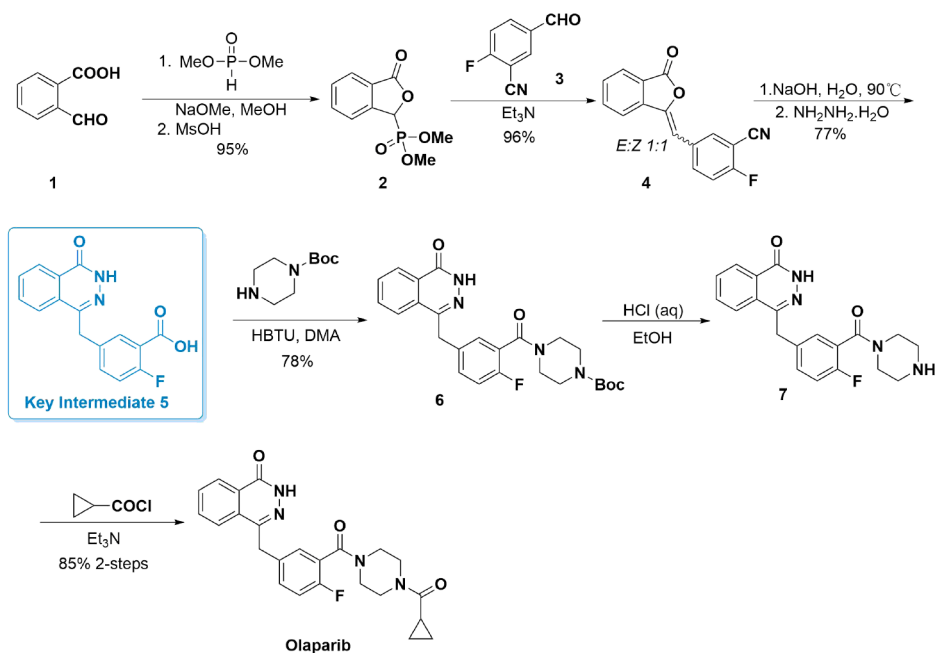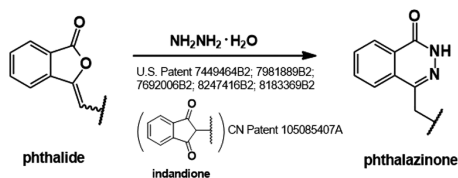
Figure 1. Three approved PARP inhibitors, olaparib, rucaparib, and niraparib.

Scheme 1. Medicinal Chemistry Route to Olaparib

Scheme 2. Formation of the Key Intermediate Phthalazinone

recommended daily dosage of olaparib tablet was 600 mg. Therefore, the maximum allowed level of hydrazine was 65 ppm in olaparib API.

The aforementioned issues with the initial synthesis prompted us to seek a new route that avoided the use of hydrazine. Herein, we report a new synthetic process for the key intermediate **5** of olaparib. As shown in Scheme 3, the low-cost phthalhydrazide as the starting material avoided the use of hydrazine by retro-synthesis analysis of the structure of olaparib. Significantly, phthalhydrazide is a usual byproduct

Scheme 3. Retro-synthesis Analysis of Olaparib
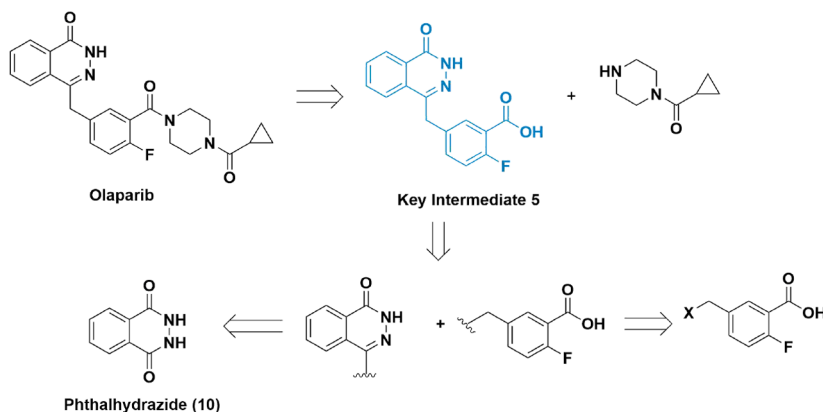
Scheme 4. Phthalhydrazide Route to Key Intermediate (5)
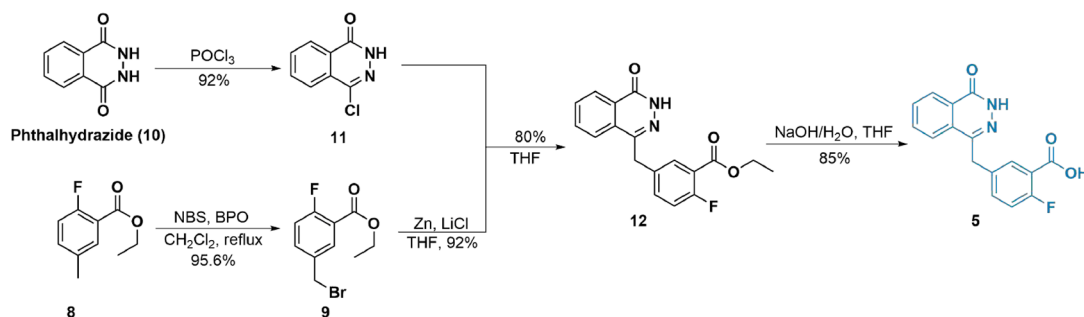
in the synthesis of many medicines, pesticides, materials, and natural products, which mainly is discarded as solid waste. It causes environmental problems that encroach on a large number of land defects and pollute groundwater. During the production of amikacin by *Qilu Pharmaceutical Co., Ltd.*, a large amount of phthalhydrazide was formed by the hydrazinolysis reaction in the last step. Based on the annual production capacity of 300 tons of amikacin, about 90 tons of phthalhydrazide is produced. Byproduct phthalhydrazide could be precipitated out from the reaction mixture, and obtained by recrystallization in MeCN.[12] Using industrial byproduct phthalhydrazide met the ICH guidelines for starting materials as a raw material[13] and efficiently avoided pollution of phthalhydrazide and waste of resources, which was in line with the principle of green chemistry that pollution prevention is better than post-pollution treatment. Meanwhile, the current route we designed effectively avoided the use of hydrazine hydrate and the related safety issues, which was in accordance with the principle of designing safe processes to prevent accidents in green chemistry.

RESULTS AND DISCUSSION

New Route to Key Intermediate (5) from Phthalhydrazide (10). We developed a convergent process to synthesize **5**, as shown in Scheme 4. Compound **10** was first converted into its corresponding monochloride product **11** using phosphorus oxychloride in 92% yield. Monobromide aryl formate (**9**) with a yield of 96% was obtained from ethyl 2-fluoro-4-methylbenzoate (**8**) with N-bromosuccinimide (NBS) and benzoyl peroxide (BPO) in dichloromethane. Negishi coupling of **11** with the zinc reagent produced by bromide **9** under zinc dust and additive LiCl afforded **12** in 80% yield. Subsequently, **5** was formed by the hydrolysis reaction in 85% yield. The overall yield for the three steps (from **10** to **5**) was 62%. The synthesis route was demonstrated on a 500 gram scale. The process mass intensity of the new synthetic route was reduced to 34.04 kg/kg intermediate **5** compared with the original route (41.73 kg/kg).

Chlorination of Phthalhydrazide (10). We first optimized the process parameters of the chlorination reaction, including chlorination reagents, chlorination reagent amount, and temperature (Table 1). Some common chlorination reagents were evaluated, including oxaloyl chloride ((COCl)₂), phosphorus oxychloride (POCl₃), and thionyl chloride (SOCl₂), but both monochloro-(**11**) and dichloro-products (**11′**) with different yields were obtained in all reactions. By contrast, 2.0 equivalent of phosphorus oxychloride showed a higher conversion than the other chlorinating reagents at reflux (entry 5), affording **11** in 35%

Table 1. Chlorination of Phthalhydrazide (10)[a]

			yield (%)[b]	
entry	chlorinated reagents (equiv)	temp. (°C)	11	11′
1	COCl₂ (2.0)	65	9	13
2	SOCl₂ (2.0)	80	12	10
3	SOCl₂ (4.0)	80	23	15
4	POCl₃ (2.0)	80	27	14
5	POCl₃ (2.0)	110	35	28
6	POCl₃ (5.0)	110	40	50
7	POCl₃ (10.0)	110	10	78

[a]Unless otherwise stated, reactions were conducted in the corresponding chlorinated reagent containing 0.06 mol **10** with stirring for 6 h. [b]Determined by high-performance liquid chromatography (HPLC) analysis.

and **11′** in 28%, respectively. Meanwhile, the scale-up synthesis routes of many APIs or intermediates involve the use of POCl₃ in the pharmaceutical industry.[14] To improve the yield of **11**, therefore, we next studied the effect of the POCl₃ amount, showing improvement of the total reaction yield with increasing amount of POCl₃ (entries 6 and 7). However, phthalhydrazide was converted into the undesired **11′** even more than **11** when the amount of POCl₃ was increased. Of the 88% total yield, for instance, **11′** was obtained in 78% yield when the reaction was performed with 10.0 equivalent POCl₃ at 110 °C (entry 7). Thus, the transformation of **11′** to **11** as a key issue was further investigated.

Partial Hydrolysis of Dichlorophthalazine (11′). Many studies have reported that similar dichlorophthalazine derivatives were hydrolyzed to chlorophthalazinone. In Weiss' work, 6-bromo-1,4-dichlorophthalazine was converted into the monochloro-product by the hydrolysis reaction in the presence of AcOH.[15] In a patent for the preparation of phthalazine derivatives, the hydrolysis of the dichlorophthalazine derivative also occurred in an alkaline environment.[16] In the workup of the chlorination, similarly, we found that the most of **11′** was readily converted into **11** by stirring the aqueous mixture overnight. After the excess phosphorus oxychloride was quenched by ice water, acidic media could facilitate the hydrolysis of dichlorophthalazine (**11′**). For example, **10** was chlorinated by 5.0 equivalent of POCl₃, affording **11** and **11′** in 40 and 50% yield, respectively. After quenching by ice water, more than 90% **11** was obtained by stirring for 12 h in acidic media. During the scale-up

manufacture (hectogram), however, the acidity produced by quenching POCl$_3$ was not enough to convert the dichloro- into monochloro-product. Thus, additional acetic acid was added to the reaction mixture to improve the conversion of **11'** to **11**. The hydrolysis of dichlorophthalazine gave only the mono-chloride product, probably because the increased electron density of monochlorophthalazine restrained further hydrolysis, affording stable 1-chloro-4-carbonylphthalazine (**11**) by keto-enol tautomerism.[17] The possible hydrolysis mechanism was the potential attack of water *via* a nucleophilic aromatic substitution type.

Bromination of Compound (8). NBS reagent is widely used in C−H bond functionalization[18] and bromination.[19] Therefore, we carried out bromination of compound **8** using NBS with a radical initiator, giving either low conversion (<50%) or the mixture with dibromide byproduct (**9'**). To improve the yield of bromination, different initiators, solvents, the amount of NBS, and reaction temperature were screened,[20,21] as shown in Table 2. Chlorinated solvents

Table 2. Bromination of Compound (8)[a]
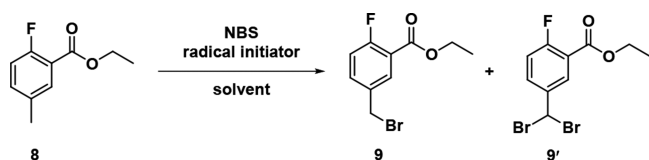
| entry	solvents	NBS (equiv)	radical initiator	temp. (°C)	yield of 9 (9') (%)[c]
1	CH$_2$Cl$_2$	1.5	light[b]	r.t.	73.2 (10.7)
2	CHCl$_3$	1.5	light	r.t.	42.8 (19.3)
3	CH$_2$Cl$_2$	1.5	AIBN (0.05 equiv)	40	41.1 (18.4)
4	CHCl$_3$	1.5	AIBN (0.05 equiv)	60	56.2 (23.8)
5	CH$_2$Cl$_2$	1.5	BPO (0.05 equiv)	40	65.4 (13.1)
6	CH$_2$Cl$_2$	1.5	BPO (0.06 equiv)	40	80.2 (9.8)
7	CH$_2$Cl$_2$	1.5	BPO (0.08 equiv)	40	85.0 (6.3)
8	CH$_2$Cl$_2$	1.5	BPO (0.1 equiv)	40	85.7 (5.7)
9	CH$_2$Cl$_2$	1.3	BPO (0.08 equiv)	40	88.1 (−)[d]
10	CH$_2$Cl$_2$	1.1	BPO (0.08 equiv)	40	95.6 (−)
11	CHCl$_3$	1.1	BPO (0.08 equiv)	60	83.8 (−)
12	CCl$_4$	1.1	BPO (0.08 equiv)	60	44.1 (−)
13	CCl$_4$	1.1	BPO (0.08 equiv)	80	51.5 (−)

[a]Unless otherwise stated, reactions were conducted in 20 mL of solvent containing 0.01 mol **8** and NBS as the brominated reagent with stirring for 6 h. [b]The reaction was initiated by irradiation using a Philips HPL-N (25 W, λ = 254 nm) lamp. [c]Determined by HPLC analysis. [d]Not detected.

were often used for the Wohl−Ziegler reaction,[22] but dibromide byproduct **9'** was easily formed in other solvents such as acetonitrile and ethyl acetate.[23] Hence, the reaction was performed in chlorinated solvents. First, the reaction was initiated under a Philips HPL-N (25 W, λ = 254 nm) lamp in CH$_2$Cl$_2$ or CHCl$_3$ at room temperature, affording the monobromide product (**9**) in 76.5 and 46.2% yield,

respectively. Given the operability of scale-up production, we further used azobisisobutyronitrile (AIBN) as a radical initiator for the bromination reaction in CH$_2$Cl$_2$ or CHCl$_3$. However, compound **9** was obtained in yield of only 41%−56% (entries 3 and 4). BPO (0.05−0.1 equiv) was used to initiate bromination of **8** in CH$_2$Cl$_2$ at 40 °C for 12 h, giving the compound **9** in 65.4−85.7% yield (entries 5−8). The results showed that dibromide byproduct was still produced in different radical initiator conditions. To suppress the production of byproduct **9'**, the amount of NBS was further optimized. The results showed that byproduct **9'** was avoided in 1.1 equiv NBS condition, and the yield of bromination reaction was increased to 95.6% (entry 10). Subsequently, we screened different solvents to purify the compound **9** by recrystallization, giving white crystal in *n*-hexane and oily in methyl tert-butyl ether and petroleum ether.

Preparation of Organozinc Reagents and Negishi Coupling Reaction. The C-C bond construction from **9** to **12** was achieved by the Negishi coupling reaction in mild conditions. Before that, benzylic bromide **9** was converted into organozinc reagent **13** by using cheap and nontoxic zinc dust, which combined good reactivity with high functional group tolerance.[24] Zinc dust was first activated with 1,2-dibromo-ethane (5%) and TMS-Cl (1%) before the reaction. 1,2-Dibromoethane could initiate the reductive insertion reaction of zinc with compound **9**, while TMS-Cl could effectively inhibit the influence of trace Pb in zinc powder on the reaction.[25] 1.5 equivalent of zinc dust was adopted from previously described optimal reaction procedures.[26] To obtain organozinc reagent with high yield, addition/reaction temperature, reaction time, and additives were screened, as summarized in Table 3. Initially, adding substrate **9** in

Table 3. Preparation of Organozinc Reagent (13)[a]
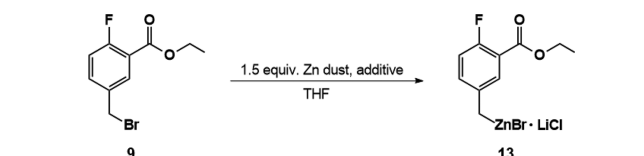
entry	temp. (°C) addition	temp. (°C) reaction	additive	time (h)	yield (%)[c]
1	r.t.	r.t.	[b]	6	[d]
2	r.t.	0		8	
3	0	r.t.		3	65
4	0	0		2.5	40
5	0	r.t.	LiCl	2	92
6	0	0	LiCl	2	60

[a]Unless otherwise stated, reactions were conducted by addition of 0.05 mol **9** to 20 mL of anhydrous THF containing 1.5 equiv zinc dust with stirring. [b]No additive. [c]Yield of the organozinc reagent was determined by iodine titration in THF solution containing anhydrate LiCl according to the previous report.[28] See Experimental Section for detailed procedure. [d]Not determined.

anhydrous THF with zinc dust at room temperature was not conductive to the formation of the organozinc reagent (entries 1 and 2). The reaction required lower addition temperature, and then warmed slowly to room temperature for the desired conversion (entries 3 and 4). In addition, the previous reports showed that LiCl considerably facilitated direct zinc insertion into alkyl, aryl, and heteroaryl iodides and bromides, and suppresses side reactions and increases the conversion.[27] Based

Table 4. Screening of Catalysis for the Negishi Coupling Reaction[a]
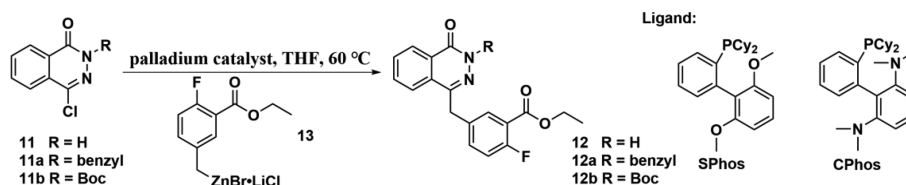
entry	substrate	catalysts[b]	yield of 12 (or 12a−b) (%)[c]
1	**11**	PdCl$_2$ (2%)	<1
2	**11**	Pd(PPh$_3$)$_4$ (2%)	32.7
3	**11**	Pd(dppf)Cl$_2$ (2%)	26.2
4	**11**	Pd(OAc)$_2$/P(Ph)$_3$ (2%)	<1
5	**11**	Pd(OAc)$_2$ (2%)/CPhos (4%)	NR[d]
6	**11**	Pd(OAc)$_2$ (2%)/CPhos (4%)	31.6
7	**11**	Pd(OAc)$_2$ (2%)/SPhos (4%)	NR
8	**11**	Pd(OAc)$_2$ (2%)/SPhos (4%)	28.5
9	**11a**	Pd(PPh$_3$)$_4$ (2%)	45.3
10	**11a**	Pd(dppf)Cl$_2$ (2%)	37.7
11	**11b**	Pd(PPh$_3$)$_4$ (2%)	38.3
12	**11b**	Pd(dppf)Cl$_2$ (2%)	29.8
13	**11**	Pd(PPh$_3$)$_4$ (4%)	52.3
14	**11**	Pd(dppf)Cl$_2$ (4%)	48.7
15	**11**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (2%/2%)	80
16	**11a**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (2%/2%)	82.2
17	**11b**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (2%/2%)	81.3
18	**11**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (1%/1%)	38.2
19	**11**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (1%/2%)	46.3
20	**11**	Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ (2%/1%)	47.7

[a]Unless otherwise stated, the organozinc reagent was added dropwise in 25 mL of anhydrous THF solution containing 30 mmol **11** (or **11a−b**) and palladium catalyst under an argon atmosphere, and the mixture was stirred at 60 °C for 6 h. [b]In the case of co-catalysts, Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ = 1:1. [c]Determined by HPLC analysis. [d]No reaction.

on the previous work, thus, LiCl (1.5 equiv) was here used as an additive to improve the insertion of equivalent zinc dust into benzylic bromide, affording organozinc reagent **13** in 92% yield (entry 5).

In order to perform a high-yield Negishi coupling reaction, various palladium catalysts were used to evaluate catalytic performance, as shown in Table 4. The screen commenced with a set of single palladium catalyst. PdCl$_2$, or Pd(OAc)$_2$ combined with the corresponding ligand P(Ph)$_3$, hardly catalyzed coupling reaction (entries 1 and 4). In the case of Pd(PPh$_3$)$_4$ or Pd(dppf)Cl$_2$, **12** was generated in 32.7 and 26.2% yield, respectively (entries 2 and 3). Meanwhile, CPhos and SPhos ligands were screened at room temperature and 60 °C in the presence of Pd(OAc)$_2$.[29] No product was obtained at room temperature, owing to the fact that compound **11** has poor solubility at room temperature in THF. Considering the solubility of substrate **11** in THF, **11** was modified by the benzyl (**11a**) or Boc (**11b**) group, respectively. Likewise, the corresponding **12a** and **12b** were obtained by single palladium catalysis in a low yield that ranged from 30 to 45% (entries 9−12). To improve the yield of Negishi coupling, the combination of Pd(PPh$_3$)$_4$ with Pd(dppf)Cl$_2$ as a palladium co-catalyst, resulted in 80% yield of the coupling product (entry 15). We found that the double-palladium catalyst could effectively improve the reaction conversion, thus Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ was selected to evaluate the catalytic performance of **11a** and **11b** as substrates. Although the solubility of the both derivatives in THF was superior to **11**, the corresponding coupling products (**12a** and **12b**) were obtained in a similar yield with **12** (entries 16 and 17). Since the modification and

removal of protective groups could affect the overall yield of the process route, the original substrate **11** directly reacted with benzylic zinc bromide **13** to give coupling product **12** in the presence of the Pd(PPh$_3$)$_4$/Pd(dppf)Cl$_2$ co-catalyst. Considering the cost of the high Pd-loading catalyst and the necessity of a double-Pd catalyst, some controlled experiments were carried out. The amount of both Pd catalysts was decreased from 2 to 1%, and **12** was obtained in only 38.2% yield (entry 18). When the loading of one of the Pd catalysts reduced to 1%, the coupling product was obtained in 46.3 and 47.7% yield, respectively (entries 19 and 20). Even if the single palladium catalyst (Pd(PPh$_3$)$_4$ or Pd(dppf)Cl$_2$) amount was increased to 4%, the yield of **12** was only 52.3 or 48.7% (entries 13 and 14). With the optimized reaction conditions in hand, we screened crystallization solvents such as ethyl acetate and *n*-hexane, acetonitrile and *n*-hexane, and methyl tert-butyl ether. The results showed that compound **12** with 99.82% HPLC and <10 ppm Pd-content (by inductively coupled plasma optical emission spectroscopy (ICP-OES), see Supporting Information Table S1) was obtained by crystallization using ethyl acetate and *n*-hexane.

■ CONCLUSIONS

In conclusion, we have developed a new and improved route to the key intermediate (**5**) of olaparib, which avoided the use of hydrazine hydrate faced with the early development route. The three-step linear route from **10** to **5** gave an overall yield of 62%. Although the yield was close to that of medicinal chemistry route, using industrial byproduct phthalhydrazide (**10**) as the starting material effectively reduced the production

cost and solved the phthalhydrazide landfill pollution to the environment. In the chlorination of phthalhydrazide, excess dichloro-product (**11′**) was directly converted into chlorophthalazinone (**11**) by acid hydrolysis during the workup process, affording **11** in 92% yield. The addition of LiCl improved the conversion of the organozinc reagent and suppressed the side reaction, as well as allowed to perform the subsequent Negishi coupling reaction in one-pot. Then, the palladium catalyst was screened to obtain an effective $Pd(PPh_3)_4/Pd(dppf)Cl_2$ co-catalyst system, affording 80% yield of **12**. This process was successfully used to yield more than 220 g of intermediate **5** with good purity. Overall, the introduction of this new route has enabled the manufacture of high-quality olaparib with excellent cost control and friendly environment, resulting in processes which we believe will be suitable for long-term commercial manufacture.

■ EXPERIMENT SECTION

Materials and Methods. General methods were used unless otherwise noted; materials were obtained from commercial suppliers and were used without further purification. Phthalhydrazide ($ 3/kg) was obtained from *Qilu Pharmaceutical Co., Ltd*. HPLC analysis was performed on Waters e2695−2998 Series (See Supporting Information for HPLC conditions). Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV-400 Nuclear Magnetic Resonance spectroscopy. Chemical shifts were expressed in ppm relative to the internal standard tetramethylsilane and coupling constants (J) in Hz. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX IV Fourier Transform Ion Cyclotron Resonance Mass spectrometer. The Pd-content was analyzed by ICP-OES using iCAP6500 (Thermo Fisher Scientific).

Preparation of the Pd-Content Analysis Sample. 0.1 g of sample was added to digestion bottle, and then 5 mL of nitric acid (65−68%) was added to the system. The system was heated to 300−400 °C to digest the organic matter. When the digestion solution becomes clear, the system is cooled to room temperature. The Pd-content of the sample dissolved in HNO_3 (5%) solution was tested by ICP-OES.

4-Chlorophthalazin-1(2H)-one (11). Phthalhydrazide (500 g, 3 mol) and phosphorus oxychloride (1.4 L, 15 mol) were added to a 5 L flask, and then the reaction mixture was stirred for 3 h at 110 °C. When the HPLC results showed that phthalhydrazide was completely consumed, the reaction was cooled to room temperature, and ice water (500 mL) was added slowly to the reaction mixture at 0∼5 °C over 1 h. Subsequently, acetic acid (1.5 L) was added to the reaction mixture followed by stirred overnight at room temperature. The precipitate was filtered and dried at 45 °C, affording compound **11** (496.8 g, 2.76 mol, 92.3%). HPLC purity: 99.14%. ^1H NMR (400 MHz, DMSO-d_6): 12.86 (s, 1H), 8.50−8.13 (m, 1H), 8.12−7.72 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): 159.56, 137.54, 134.98, 133.48, 128.79, 126.97, 125.95. HRMS (ESI) m/z: calcd for $C_8H_6ClN_2O$ $[M + H]^+$: 181.2359, found: 181.2351.

2-Benzyl-4-chlorophthalazin-1(2H)-one (11a). A 100 mL flask was charged with **11** (2 g, 11 mmol), K_2CO_3 (3 g, 22 mmol) and THF (40 mL). Benzyl bromide (1.96 mL, 16.4 mmol) was added to the reaction mixture, and then the reaction was heated to 70 °C. When TLC analysis showed that the raw material disappears, the reaction was cooled to 25 °C and the reaction mixture was quenched by water (20 mL). The reactants were extracted using ethyl acetate (20 mL) followed by removing the organic solvent under reduced pressure. The residues were crystallized with petroleum ether and ethyl acetate (20:1), affording light yellow 2-benzyl-4-chlorophthalazin-1(2H)-one (2 g, 8.4 mmol, 80%). ^1H NMR (400 MHz, DMSO-d_6): 8.05 (dd, J = 6.7, 1.4 Hz, 1H), 8.02−7.96 (m, 3H), 7.35−7.26 (m, 5H), 5.31 (s, 2H). HRMS (ESI) m/z: calcd for $C_{15}H_{12}ClN_2O$ $[M + H]^+$: 271.0638, found: 271.0643.

Tert-butyl 4-chloro-1-oxophthalazine-2(1H)-carboxylate (11b). **11** (2 g, 11 mmol) and triethylamine (4 mL) were added to a 100 mL flask with dichloromethane (50 mL). $(Boc)_2O$ (2.5 g, 11.5 mmol) in dichloromethane (5 mL) was added to the reaction mixture within 10 min at room temperature, and then the reaction was stirred for 1 h. When TLC analysis showed that the material concentration had not change, the reaction mixture was washed with water (60 mL). After separation, the organic solvent was removed under reduced pressure. White solid tert-butyl-4-chloro-1-oxophthalazine-2(1H)-carboxylate was obtained by column chromatography separation (1.05 g, 3.74 mmol, 34%). ^1H NMR (400 MHz, DMSO-d_6): 8.29 (d, J = 7.2 Hz, 1H), 8.08−8.04 (m, 1H), 7.99 (t, J = 13.2 Hz, 1H), 1.58 (s, 9H). HRMS (ESI) m/z: calcd for $C_{13}H_{14}ClN_2O_3$ $[M + H]^+$: 281.0693, found: 281.0697.

Ethyl 5-(bromomethyl)-2-fluorobenzoate (9). To a 10 L reactor with a condenser, ethyl 2-fluoro-5-methylbenzoate (500 g, 2.7 mol), BPO (56 g, 0.23 mol), and CH_2Cl_2 (500 mL) was added under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and then NBS (525 g, 2.97 mol) was added in three batches. During the addition of NBS, the reaction inner temperature was kept in the range between 10 and 20 °C. After the inner temperature of the reaction dropped and stabilized, the reaction mixture was stirred for 12 h at 40 °C. When HPLC analysis indicated the reaction completion, the reaction mixture was washed with 10% of Na_2SO_3 aqueous solution (250 mL) and water (1.5 L), respectively. Then, the water phase was extracted with CH_2Cl_2 (1.5 L × 2). The combined organic solvent was concentrated under reduced pressure to 500 mL (1 rel vols), and n-hexane (600 mL) was added. Then the solution was concentrated to 300 mL (1 rel vols), and n-hexane (1.7 L, 3.4 rel vols) was added. Compound **9** (673 g, 2.58 mol, 96%) was obtained by recrystallization using n-hexane (2 L). HPLC purity: 95.36%. ^1H NMR (400 MHz, CDCl$_3$): 7.95 (dd, J = 6.7, J = 2.4 Hz, 1H), 7.59−7.55 (m, 1H), 7.12 (dd, J = 10.2, J = 8.6 Hz, 1H), 4.48 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$): 163.79, 162.87, 160.27, 134.92, 133.85, 132.59, 117.74, 61.54, 31.64, 14.25. HRMS (ESI) m/z: calcd for $C_{10}H_{11}BrFO_2$ $[M + H]^+$: 260.9926, found: 260.9925.

(3-(Ethoxycarbonyl)-4-fluorophenyl)zinc(II) bromide (13). Zinc dust (150 g, 2.3 mol) and LiCl (69 g, 1.65 mol) were added to a 3 L flask with anhydrous THF (600 mL) under a N_2 atmosphere. Then, 1,2-dibromoethane (5%) was added to the reaction and the reaction mixture was heated to 66 °C until ebullition occurs. The reaction mixture was cooled to 25 °C, and then trimethylsilyl chloride (1%) was added to the reaction mixture. The reaction was heated again until ebullition occurs followed by cooling to 0 °C. Compound **9** (300 g, 1.1 mol) dissolved in THF (600 mL) was slowly added to the reaction mixture at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 20 min at 0 °C followed by stirring for 2 h at 25 °C. The reaction solution (1 mL) was added dropwise to THF solution of iodine (0.9 mmol) with

LiCl via syringe, and the brown color of iodine in THF solution disappeared indicating the production of compound **13**.[28] The concentration of the organozinc reagent was 0.88 mol/L, and the yield of **13** was 92.5%.

Ethyl 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)-methyl)benzoate (12). **11** (200 g, 1.1 mol), tetrakis-(triphenylphosphine)palladium (40 g, 2%), and [1,1'-Bis-(diphenylphosphino) ferrocene]dichloropalladium (40 g, 2%) were added to a flask containing anhydrous THF (1 L). **13** (1.2 L) in THF was added to the reaction mixture over 3 h at room temperature under a N$_2$ atmosphere. The reaction was stirred for 6 h at 60 °C, and then quenched with methanol (400 mL) followed by the mixture being filtered using diatomite. Five percent activated carbon was added to the mixture and stirred for 30 min followed by activated carbon. The organic solvent was concentrated under reduced pressure to 400 mL, and then ethyl acetate (800 mL) was added to the reaction mixture followed by the solution concentrated to 400 mL. Hexane was slowly added to the mixture, and when the reaction system became turbid, the reaction was cooled to 0 °C for 3 h followed by filtration, affording 2-fluoro-5-[(4-carbonyl-3,4-dihydrophthalazine-1-yl)methyl]benzoate (287 g, 0.88 mol, 79.8%). HPLC purity: 99.12%. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.30 (dd, J = 7.8, J = 1.0 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.93−7.80 (m, 3H), 7.63−7.54 (m, 1H), 7.36−7.21 (m, 6H), 5.32 (s, 2H), 4.39 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d$_6$): 161.42, 159.81, 158.88, 145.33, 135.85, 135.76, 134.93, 134.03, 132.13, 132.08, 129.54, 128.31, 126.53, 131.63, 131.55, 129.03, 125.91, 118.81, 118.71, 117.69, 117.47, 61.56, 36.69, 14.54. HRMS (ESI) m/z: calcd for C$_{18}$H$_{16}$FN$_2$O$_3$ [M + H]$^+$: 327.1145, found: 327.1130. Pd-content: 5.480 ppm by ICP-OES.

Ethyl 5-((3-benzyl-4-oxo-3,4-dihydrophthalazin-1-yl)-methyl)-2-fluorobenzoate (12a). **11a** (0.8 g, 2.96 mmol) and tetrakis(triphenylphosphine)palladium (2%) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (2%) were added to a flask with anhydrous THF (20 mL) under N$_2$. **13** in THF (2.5 mL) was added slowly to the reaction mixture and then warmed to 60 °C. After agitation for 6 h, the reaction was quenched with methanol. The reaction mixture was filtered by diatomite, and then the organic solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **12a** (1 g, 2.4 mmol, 82.2%). ^{1}H NMR (400 MHz, DMSO-d$_6$): 8.29 (d, J = 7.7, 1H), 7.99 (d, J = 8.9 Hz, 1H), 7.92−7.82 (m, 3H), 7.61−7.56 (m, 1H), 7.31−7.22 (m, 6H), 5.31 (s, 2H), 4.38 (s, 2H), 4.30−4.28 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H). HRMS (ESI) m/z: calcd for C$_{25}$H$_{22}$FN$_2$O$_3$ [M + H]$^+$: 417.1609, found: 417.1618.

2-Fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)-methyl)benzoic acid (5). **12** (300 g, 0.9 mol) and 1 mol/L sodium hydroxide solution (1 L) were added to 3 L flask containing THF (600 mL). The reaction mixture was stirred at room temperature for 12 h, and then HPLC analysis indicated the reaction completion. The solution was concentrated under reduced pressure to 1 L, and then 1 mol/L hydrochloric acid was used to adjust the pH of the reaction mixture to 6∼7. The resulting precipitate was filtered, and the solid was washed with water (100 mL) and dried at 45 °C to give compound **5** (227.97 g, 0.76 mol, 84.7%). HPLC purity: 99.82%. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.23 (s, 1H), 12.60 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 7.5 Hz,

1H), 7.87−7.80 (m, 1H), 7.58 (d, J = 3.8 Hz, 1H), 7.29−7.20 (m, 1H), 4.36 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d$_6$): 165.54, 161.69, 159.88, 159.14, 145.44, 135.46, 134.82, 134.08, 132.38, 132.11, 129.58, 128.38, 126.59, 125.98, 119.72, 117.64, 110.00, 36.80. HRMS (ESI) m/z: calcd for C$_{16}$H$_{10}$FN$_2$O$_3$ [M-H]$^−$: 297.0675, found: 297.0692.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06920.

General analytical methods and available copies of ^{1}H NMR, ^{13}C NMR, HRMS, and HPLC chromatograms for compound **9**, **9′**, **11**, **11′**, **11a**, **11b**, **12**, **12a,** and **5**; result of the Pd-content analysis of compound **12** (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PARP, poly(ADP-ribose) polymerase; BRCA, breast cancer; Boc, tert-butoxycarbonyl; BPO, benzoyl peroxide; NBS, *N*-

bromosuccinimide; AIBN, azodiisobutyronitrile; HPLC, high-performance liquid chromatography; TLC, thin layer chromatography; THF, tetrahydrofuran

■ REFERENCES

(1) Fong, P. C.; Boss, D. S.; Yap, T. A.; Tutt, A.; Wu, P. G.; Mergui-Roelvink, M.; Mortimer, P.; Swaisland, H.; Lau, A.; O'Connor, M. J.; Ashworth, A.; Carmichael, J.; Kaye, S. B.; Schellens, J. H. M.; de Bono, J. S. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N. Engl. J. Med.* **2009**, *361*, 123−134.

(2) Farmer, H.; McCabe, N.; Lord, C. J.; Tutt, A. N. J.; Johnson, D. A.; Richardson, T. B.; Santarosa, M.; Dillon, K. J.; Hickson, I.; Knights, C.; Martin, N. M. B.; Jackson, S. P.; Smith, G. C. M.; Ashworth, A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* **2005**, *434*, 917−921.

(3) Lord, C. J.; Ashworth, A. PARP inhibitors: synthetic lethality in the clinic. *Science* **2017**, *355*, 1152−1158.

(4) Mylavarapu, S.; Das, A.; Roy, M. Role of BRCA mutations in the modulation of response to platinum therapy. *Front. Oncol.* **2018**, *8*, 1−11.

(5) Kim, G.; Ison, G.; McKee, A. E.; Zhang, H.; Tang, S.; Gwise, T.; Sridhara, R.; Lee, E.; Tzou, A.; Philip, R.; Chiu, H. J.; Ricks, T. K.; Palmby, T.; Russell, A. M.; Ladouceur, G.; Pfuma, E.; Li, H.; Zhao, L.; Liu, Q.; Venugopal, R.; Ibrahim, A.; Pazdur, R. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin. Cancer Res.* **2015**, *21*, 4257−4261.

(6) (a) Martin, N. M. B.; Smith, G. C.; Jackson, S. P.; Loh, V. J. M.; Cockcroft, X.-L. F.; Matthews, I. T. W.; Menear, K. A.; Kerrigan, F.; Ashworth, A. Phthalazinone Derivatives. U.S. Patent Appl. 7449464 B2, November 11, 2008. (b) Martin, N. M. B.; Smith, G. C.; Jackson, S. P.; Loh, V. J. M.; Cockcroft, X.-L. F.; Matthews, I. T. W.; Menear, K. A.; Kerrigan, F.; Ashworth, A. Phthalazinone Derivatives. U.S. Patent Appl. 7981889 B2, July 19, 2011. (c) Martin, N. M. B.; Smith, G. C.; Jackson, S. P.; Loh, V. J. M.; Cockcroft, X.-L. F.; Matthews, I. T. W.; Menear, K. A.; Kerrigan, F.; Ashworth, A. Phthalazinone Derivatives. U.S. Patent Appl. 7981889 B2, December 16, 2014. Medicinal Chemistry route summarized in the following review (d) Flick, A. C.; Ding, H. X.; Leverett, C. A.; Kyne, R. E.; Liu, K. K. C.; Fink, S. J.; O'Donnell, C. Synthetic approaches to the 2014 new drugs. *Bioorg. Med. Chem.* **2016**, 1937−1980.

(7) (a) Menear, K. A.; Ottridge, A. P.; Londesbrough, D. J.; Hallett, M. R.; Mulholland, K. R.; Pittam, J. D.; Laffan, D. D. P.; Ashworth, I. W.; Jones, M. F.; Cherryman, J. H. Phthalazinone Derivatives. U.S. Patent Appl. 7692006 B2, April 6, 2010. (b) Menear, K. A.; Ottridge, A. P.; Londesbrough, D. J.; Hallett, M. R.; Mulholland, K. R.; Pittam, J. D.; Laffan, D. D. P.; Ashworth, I. W.; Jones, M. F.; Cherryman, J. H. Phthalazinone derivatives. U.S. Patent Appl. 8247416 B2, August 21, 2012.

(8) Quigley, K. A.; Still, E. J.; Chyall, L. J. 4-[3-(4-Cyclopropanecarbonyl- piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one. U.S. Patent Appl. 8183369 B2, May 22, 2012.

(9) Hughes, D. L. Patent review of manufacturing routes to recently approved PARP inhibitors: olaparib, rucaparib, and niraparib. *Org. Process Res. Dev.* **2017**, *21*, 1227−1244.

(10) Scott, F. E.; Burns, J. J.; Lewis, B. *Explosive Properties of Hydrazine, Report of Investigations 4460*; U.S. Dept. of the Interior: Bureau of Mines, Pittsburgh, PA, 1949.

(11) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S9/Step4/S9_Step4_Guideline.pdf (accessed August 1, 2021)

(12) (a) Behniafar, H.; Ahmadi-khaneghah, A.; Yazdi, M. Enhanced heat stability and storage modulus in novel PTMO-intercalated clay platelets/PTMO-based polyurethane nanocomposites. *J. Polym. Res.* **2016**, *23*, 202. (b) Li, X.; Youells, S.; Russell, R. K.; Roessler, A.; Schmid, T.; Faessler, R.; Weidner-Wells, M. A.; Grant, E. B.; Macielag, M. J. An Improved Non-chromatographic Scale-up Synthesis of a New 1,6,7,8-Substituted-4-oxo-1,4-dihydroquinoline-

3-carboxylic Acid as a Potent Bacterial Topoisomerase Inhibitor. *Org. Prep. Proced. Int.* **2010**, *42*, 151−160. (c) Wang, S. C.; Zhang, K.; Cai, C. W.; Chu, J.; Sun, Z. J.; Bu, S. S.; Sun, X. X.; Wang, F. Y. A kind of synthetic method of amikacin. CN Patent Appl. 106866755 B, March 13, 2017.

(13) https://database.ich.org/sites/default/files/Q11%20Guideline.pdf. (accessed August 1, 2021)

(14) (a) Frutos, R. P.; Tampone, T. G.; Mulder, J. A.; Rodriguez, S.; Yee, N. K.; Yang, B.-S.; Senanayake, C. H. Development of a Practical Process for the Synthesis of PDE4 Inhibitors. *Org. Process Res. Dev.* **2016**, *20*, 982−988. (b) Yamagami, T.; Kobayashi, R.; Moriyama, N.; Horiuchi, H.; Toyofuku, E.; Kadoh, Y.; Kawanishi, E.; Izumoto, S.; Hiramatsu, H.; Nanjo, T.; Sugino, M.; Utsugi, M.; Moritani, Y. Scalable Process Design for a PDE10A Inhibitor Consisting of Pyrazolopyrimidine and Quinoxaline as Key Units. *Org. Process Res. Dev.* **2019**, *23*, 578−587. (c) Zell, D.; Dalziel, M. E.; Carrera, D. E.; Stumpf, A.; Bachmann, S.; Mercado-Marin, E.; Koenig, S. G.; Zhang, H.; Gosselin, F. An Efficient Second-Generation Manufacturing Process for the pan-RAF Inhibitor Belvarafenib. *Org. Process Res. Dev.* **2021**, *25*, 2338−2350.

(15) Weiss, M. M.; Dineen, T. A.; Marx, I. E.; Altmann, S.; Boezio, A.; Bregman, H.; Chu-Moyer, M.; DiMauro, E. F.; Bojic, E. F.; Foti, R. S.; Gao, H.; Graceffa, R.; Gunaydin, H.; Guzman-Perez, A.; Huang, H. B.; Huang, L. Y.; Jarosh, M.; Kornecook, T.; Kreiman, C. R.; Ligutti, J.; La, D. S.; Lin, M. H. J.; Liu, D.; Moyer, B. D.; Nguyen, H. N.; Peterson, E. A.; Rose, P. E.; Taborn, K.; Youngblood, B. D.; Yu, V.; Fremeau, R. T. Sulfonamides as Selective Na(V)1.7 Inhibitors: Optimizing Potency and Pharmacokinetics While Mitigating Metabolic Liabilities. *J. Med. Chem.* **2017**, *60*, 5969−5989.

(16) Araldi, G.; Ronsheim, M.; Ronsheim, M. Phthalazine derivatives. U.S. Patent Appl. 8044041 B2, October 25, 2011.

(17) Monsieurs, K.; Tapolcsányi, P.; Loones, K. T. J.; Neumajer, G.; Dirk De Ridder, J. A.; Goubitz, K.; Lemière, G. L. F.; Dommisse, R. A.; Mátyus, P.; Maes, B. U. W. Is samoquasine A indeed benzo[*f*]phthalazin-4(3*H*)-one? Unambiguous, straightforward synthesis of benzo[*f*]phthalazin-4(3*H*)-one and its regioisomer benzo-[*f*]phthalazin-1(2*H*)-one. *Tetrahedron* **2007**, *63*, 3870−3881.

(18) Wang, H.; Wang, Z.; Wang, Y. W.; Zhou, R. R.; Wu, G. C.; Yin, S. Y.; Yan, X.; Wang, B. N-Bromosuccinimide (NBS)-Catalyzed C−H Bond Functionalization: An Annulation of Alkynes with Electron Withdrawing Group (EWG)-Substituted Acetyl Indoles for the Synthesis of Carbazoles. *Org. Lett.* **2017**, *19*, 6140−6143.

(19) Djerassi, C. Brominations with N-Bromosuccinimide and Related Compounds. The Wohl-Ziegler Reaction. *Chem. Rev.* **1948**, *43*, 271−317.

(20) Mishra, J. K.; Garg, P.; Dohare, P.; Kumar, A.; Siddiqi, M. I.; Ray, M.; Panda, G. Amino acid-based enantiomerically pure 3-substituted 1,4-benzodiazepin-2-ones: A new class of anti-ischemic agents. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1326−1331.

(21) Amati, A.; Dosualdo, G.; Zhao, L.; Bravo, A.; Fontana, F.; Minisci, F.; Bjorsvik, H. R. Catalytic processes of oxidation by hydrogen peroxide in the presence of Br$_2$ or HBr. Mechanism and synthetic applications. *Org. Process Res. Dev.* **1998**, *2*, 261−269.

(22) (a) Baird, L. J.; Colomban, C.; Turner, C.; Teesdale-Spittle, P. H.; Harvey, J. E. Alkenylphosphonates: unexpected products from reactions of methyl 2-[(diethoxyphosphoryl)methyl]benzoate under Horner−Wadsworth−Emmons conditions. *Org. Biomol. Chem.* **2011**, *9*, 4432−4435. (b) Li, Q.; Meng, L.; Zhou, S.; Deng, X.; Wang, N.; Ji, Y.; Peng, Y.; Xing, J.; Yao, G. Rapid generation of novel benzoic acid-based xanthine derivatives as highly potent, selective and long acting DPP-4 inhibitors: Scaffold-hopping and prodrug study. *Eur. J. Med. Chem.* **2019**, *180*, 509−523. (c) Liu, H.; Chen, L.; Zhou, F.; Zhang, Y. X.; Xu, J.; Xu, M.; Bai, S. P. Anti-oligomerization sheet molecules: Design, synthesis and evaluation of inhibitory activities against alpha-synuclein aggregation. *Bioorg. Med. Chem.* **2019**, *27*, 3089−3096.

(23) Zhou, Z.; Wang, Z.; Kou, J.; Wu, S.; Zhang, J.; Yuan, X.; Wu, X.; Li, C.-H.; Liao, G. Development of a Quality Controllable and Scalable Process for the Preparation of 7,8-Difluoro-6,11-

dihydrodibenzo[b,e]thiepin-11-ol: A Key Intermediate for Baloxavir Marboxil. *Org. Process Res. Dev.* **2019**, *23*, 2716−2723.

(24) Huang, W.; Ye, J. L.; Zheng, W.; Dong, H. Q.; Wei, B. G. Radical migration-addition of *N*-tert-butanesulfinyl imines with organozinc reagents. *J. Org. Chem.* **2013**, *45*, 11229−11237.

(25) (a) Ender, E. Use of activation methods for organozinc reagents. *Tetrahedron* **1987**, *43*, 2203−2212. (b) Takai, K.; Kakiuchi, T.; Utimoto, K. A Dramatic Effect of a Catalytic Amount of Lead on the Simmons-Smith Reaction and Formation of Alkylzinc Compounds from Iodoalkanes. Reactivity of Zinc Metal: Activation and Deactivation. *J. Org. Chem.* **1994**, *59*, 2671−2673.

(26) Metzger, A.; Schade, M. A.; Manolikakes, G.; Knochel, P. A general preparation of polyfunctional benzylic zinc organometallic compounds. *Chem.-Asian J.* **2008**, *3*, 1678−1691.

(27) Metzger, A.; Schade, M. A.; Knochel, P. LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides. *Org. Lett.* **2008**, *10*, 1107−1110.

(28) Krasovskiy, A.; Knochel, P. Convenient titration method for organometallic zinc, magnesium, and lanthanide reagents. *Synthesis* **2006**, *2006*, 0890−0891.

(29) Oderinde, M. S.; Mao, E.; Ramirez, A.; Pawluczyk, J.; Jorge, C.; Cornelius, L. A. M.; Kempson, J.; Vetrichelvan, M.; Pitchai, M.; Gupta, A.; Gupta, A. K.; Meanwell, N. A.; Mathur, A.; Dhar, T. G. M. Synthesis of Cyclobutane-Fused Tetracyclic Scaffolds via Visible-Light Photocatalysis for Building Molecular Complexity. *J. Am. Chem. Soc.* **2020**, *142*, 3094−3103.