ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

pubs.acs.org/OPRD

Article

Development and Scale-Up of an Asymmetric Synthesis Process for Alogliptin

Masatoshi Yamada,* Sayuri Hirano, Ryoji Tsuruoka, Masahiro Takasuga, Kenichi Uno, Kotaro Yamaguchi, and Mitsuhisa Yamano

Cite This: *Org. Process Res. Dev.* 2021, 25, 327−336

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

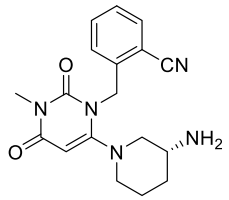
ABSTRACT: Alogliptin (**1**) benzoate is a potent, highly selective inhibitor of serine protease dipeptidyl-peptidase IV, approved by US FDA for the treatment of type 2 diabetes. Herein, we report a more cost-effective process that includes ruthenium-catalyzed asymmetric hydrogenation followed by Hofmann rearrangement of 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (**10**) to introduce a chiral amino moiety at a late stage. Use of an inexpensive and readily available nicotinamide (**6**) for a chiral aminopiperidine core and iodobenzene diacetate (PIDA) under mild and specific conditions allowed us to access **1** with excellent total yield and comparable quality to that manufactured by the original process.

KEYWORDS: *asymmetric hydrogenation, enamide, Hofmann rearrangement, PIDA, alogliptin, trelagliptin*

INTRODUCTION

Takeda Pharmaceutical Company subsidiary Takeda San Diego (formerly Syrrx) disclosed 2-{6-[3(*R*)-amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-ylmethyl}-benzonitrile (alogliptin, **1**) as a dipeptidyl peptidase IV (DPP-4) inhibitor and an agent for the treatment of type 2 diabetes mellitus (Scheme 1).[1−3] Alogliptin inhibits DPP-4, which normally degrades the incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). The inhibition of DPP-4 increases the amount of active plasma incretins, which helps with glycemic control. GIP and GLP-1 stimulate glucose-dependent secretion of insulin in pancreatic β cells. GLP-1 has the additional effects of suppressing glucose-dependent glucagon secretion, inducing satiety, reducing food intake, and reducing gastric emptying.[4] Alogliptin or a fixed dose combination with the antidiabetic agent metformin hydrochloride was approved and launched first in Japan in 2010 and is now commercially available in many countries, including Australia, China, Europe, Japan, Mexico, South Korea, and the United States, under varying brand names.[5]

Scheme 1. Chemical Structure of Alogliptin (1)



1
(Alogliptin)

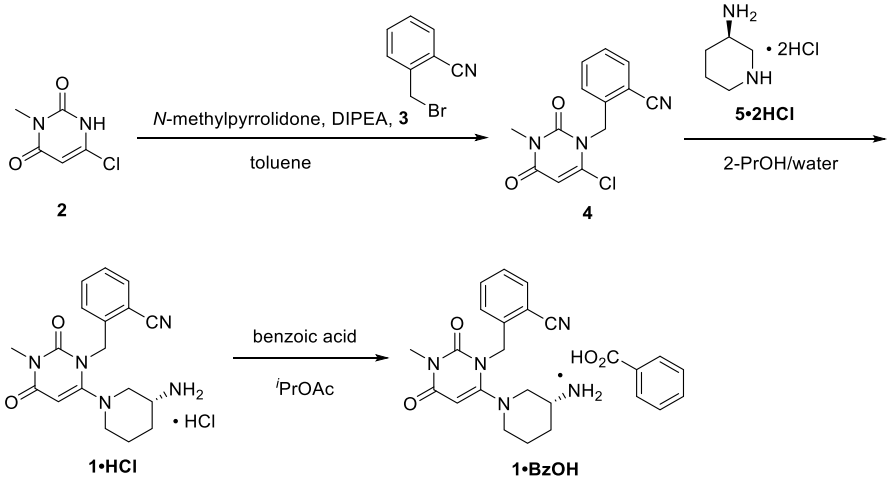
The original process for the synthesis of alogliptin starts with condensation of 6-chloro-3-methyluracil (**2**) and α-bromotoluoylnitrile (**3**) to give the key intermediate **4**. Then, (*R*)-3-aminopiperidine (**5**) is introduced to **4** by nucleophilic substitution, followed by salt formation with benzoic acid to afford alogliptin (Scheme 2).[2]

With growing demand around the world, it was considered that a more efficient and cost-effective process for alogliptin would be beneficial. Among the starting materials of the original process, the optically active amine **5**, a relatively expensive material, has mainly been synthesized *via* inefficient routes employing optical resolution, with yields of 50% at most.[6] We envisioned that an alternative process, where the chiral stereocenter is constructed *via* an asymmetric method, would improve the total yield and streamline the process. The atom economical enantioselective approach would also enable reduction of the raw material cost of alogliptin. Herein, we report a new efficient asymmetric process for the synthesis of alogliptin. A key transformation is asymmetric hydrogenation of 1,4,5,6-tetrahydropyridine-3-carboxamide (**7**), which is synthesized in a single step from the readily available and low-cost nicotinamide (**6**). We found that ruthenium catalysis in the presence of strong acids was highly effective for the transformation. After condensation with a pyrimidine-2,4-dione core, an amide moiety was transformed into an amine without erosion of enantioselectivity *via* Hofmann rearrangement, using iodobenzene diacetate (PIDA) as an oxidizing agent.[7]

Received: December 19, 2020
Published: February 10, 2021

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Scheme 2. Original Synthetic Process of Alogliptin (1) Benzoate



Scheme 3. Partial Reduction of 6

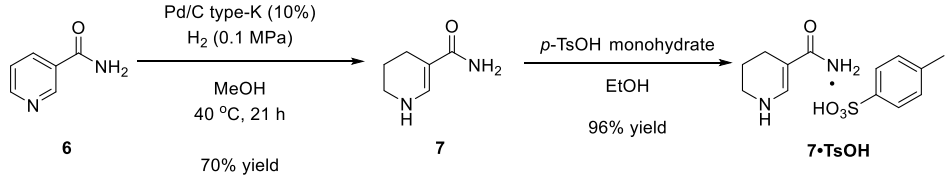
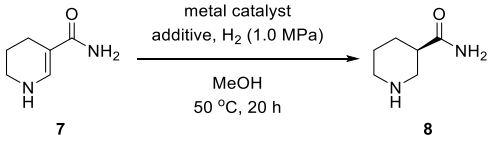


Table 1. Asymmetric Hydrogenation of 7[a]



entry	metal precursor	ligand	s/c[b]	additive[c]	conversion (%)[d]	% ee[e]
1	$[RhCl(cod)]_2$	(*R*)-BINAP	20		74	racemic
2	$[IrCl(cod)]_2$	(*R*)-BINAP	20		67	racemic
3	$Pd(OAc)_2$	(*R*)-BINAP	20		0	
4	$RuCl_2$\{(*R*)-binap\}		20		39	−59
5	$RuCl_2$\{(*R*)-binap\}		20	CH_3CO_2H	84	−15
6	$RuCl_2$\{(*R*)-binap\}		20	$PhCO_2H$	61	−12
7	$RuCl_2$\{(*R*)-binap\}		20	$PhSO_3H$	100	−70
8	$RuCl_2$\{(*R*)-binap\}		20	*p*-TsOH·H_2O	100	−70
9	$RuCl_2$\{(*R*)-binap\}$(dmf)_n$		100	*p*-TsOH·H_2O	100	−68
10	$RuCl_2$\{(*S*)-binap\}$(dmf)_n$		100	*p*-TsOH·H_2O	100	69
11	$RuCl_2$\{(*R,S*)-mandyphos\}$(dmf)_n$		100	*p*-TsOH·H_2O	100	−69
12	$RuCl_2$\{(*R,S*)-xylyl-mandyphos\}$(dmf)_n$		100	*p*-TsOH·H_2O	100	−81
13	$RuCl_2$\{(*R*)-phanephos\}$(dmf)_n$		100	*p*-TsOH·H_2O	100	−86

[a]Unless otherwise stated, reactions were conducted under 1 MPa of H_2 for 20 h at 50 °C using **7** in MeOH containing a metal complex. [b]Substrate-to-catalyst molar ratio. [c]1 equivalent of **7**. [d]Determined by chiral high-performance liquid chromatography (HPLC) analysis, with the conditions: SHISEIDO CD-Ph column (5 μm, 250 × 4.6 mm), 0.1 M aq KPF_6/MeCN 95/5, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 200 nm (UV), t_R: 13.7 min (**7**), t_R: 15.2 min (***ent*-8**), and t_R: 17.0 min (**8**). [e]Assayed by chiral HPLC analysis, with the conditions: CHIRALPAK IC column (5 μm, 250 × 4.6 mm), MeCN/0.02 M aq H_3PO_4 3/7, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 200 nm (UV), The sample was derived to benzoylated form, t_R: 13.1 min (*N*-benzoylated ***ent*-8**), and t_R: 17.2 min (*N*-benzoylated **8**).

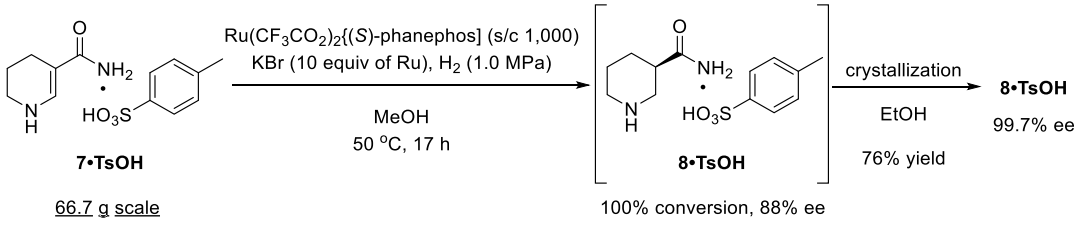
RESULTS AND DISCUSSION

Partial Reduction of Nicotinamide (6). The classical method for the partial reduction of **6** into **7** with Pd/C as a heterogeneous hydrogenation catalyst has been reported to proceed in 70−92% yield.[8] Optimization of the partial reduction was investigated, to suppress over-reduction to racemic nipecotamide (**8**). The stirring speed and hydrogen pressure in the reaction mixture were found to be important to obtain **7** in acceptable yield with constant reproducibility.

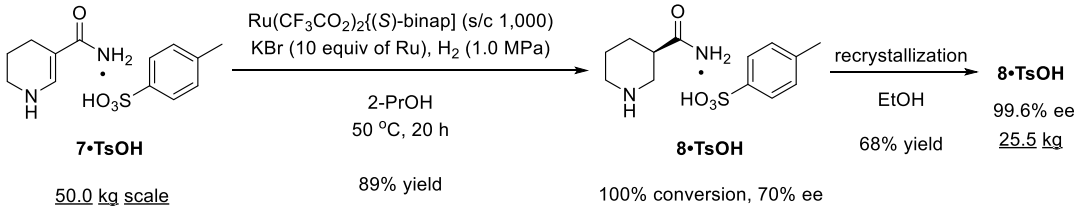
Transformation of **6** to **7** was carried out with Pd/C type-K, purchased from N.E. CHEMCAT Corporation, in MeOH under 0.1 MPa of hydrogen pressure at 40 °C for 21 h. Although the reaction gave a mixture in the ratio of **6**/**7**/**8** = 1/77/22, **7** was successfully isolated in 70% yield after crystallization from MeOH. Enamide **7** was then converted to its mono *p*-

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Scheme 4. Asymmetric Hydrogenation of 7·TsOH with $Ru(CF_3CO_2)_2\{(S)$-Phanephos$\}$ at s/c 1000

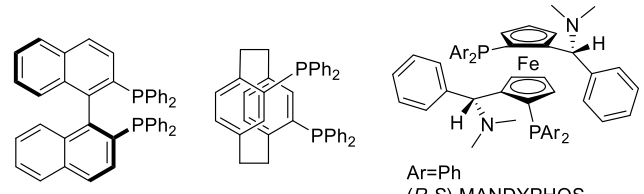


Scheme 5. Large-Scale Asymmetric Hydrogenation of 7·TsOH with $Ru(CF_3CO_2)_2\{(S)$-Binap$\}$ at s/c 1000



toluenesulfonate as a 0.85 ethanol solvate, with 96% yield from EtOH, for the next asymmetric hydrogenation step (Scheme 3). On a 70 kg scale of **6**, **7·TsOH** was obtained in 60% yield in two steps and used directly in the next step as a substrate for asymmetric hydrogenation.

Asymmetric Hydrogenation of 1,4,5,6-Tetrahydropyridine-3-carboxamide (7). We first designed a small screen to assess the feasibility of asymmetric hydrogenation of enamide **7** to hydrogenation product **8**. To our knowledge, transition metal-catalyzed asymmetric hydrogenation of 7-like non-protected tetrahydropyridines has not been reported, although some catalytic examples for 3-carboxy-protected 1,4,5,6-tetrahydropyridines were recorded with good enantioselectivity.[9] The screen commenced with a relatively small set of commercially available chiral transition metal catalysts (Table 1). The combination with (*R*)-BINAP and $[RhCl(cod)]_2$ or $[IrCl(cod)]_2$ resulted in moderate conversion with no enantioselectivity (Table 1, entries 1 and 2). The combination with (*R*)-BINAP and $Pd(OAc)_2$ provided a negligible amount of **8** (entry 3). In the case of $RuCl_2\{(R)$-binap$\}$, **8** was generated in 39% conversion with moderate enantioselectivity (−59% ee, entry 4). In the asymmetric hydrogenation of **7**, addition of Bronsted acid was found to be very effective to improve the reaction conversion (entries 5 and 6). Among the Bronsted acids tested, sulfonic acids such as benzenesulfonic acid and *p*-toluenesulfonic acid monohydrate achieved full conversion of **7** to provide **8** with −70% ee (entries 7 and 8). We selected *p*-toluenesulfonic acid monohydrate as an acid additive and subsequently evaluated the performance of various chiral diphosphine ligands, as depicted in entries 9−13. The corresponding chiral ruthenium catalyst was prepared as a dimethylformamide (DMF) complex according to the classical method.[10] $RuCl_2\{(R)$-binap$\}(dmf)_n$ gave the same result as that in entry 8 at s/c (substrate-to-catalyst molar ratio) 100 (entry 9). When $RuCl_2\{(S)$-binap$\}(dmf)_n$ was employed, the enantioselectivity was completely reversed, and the desired configuration of **8** was obtained with 69% ee (entry 10). In the screening of 44 types of chiral diphosphine ligands, $RuCl_2\{(R,S)$-mandyphos$\}(dmf)_n$ showed the same performance as (*R*)-BINAP (entry 11). The use of (*R,S*)-Xylyl-MANDYPHOS and (*R*)-PHANEPHOS showed the best results, giving **8** in 81% ee and 86% ee, respectively (entries 12 and 13).



In 1998, Pye *et al.* reported a practical and reproducible procedure using the readily prepared [2.2]-PHANEPHOS-Ru(II)bistrifluoroacetate salt, $Ru(CF_3CO_2)_2\{(S)$-phanephos$\}$, in the presence of tetrabutylammonium iodide (TBAI), that allowed the asymmetric hydrogenation of *β*-ketoesters up to 96% ee.[11] Moreover, they mentioned that $Ru(CF_3CO_2)_2\{(S)$-phanephos$\}$could be stored up to several weeks in an argon atmosphere without noticeable deterioration from a practical standpoint. We prepared $Ru(CF_3CO_2)_2\{(S)$-phanephos$\}$ according to the literature[11] and conducted an optimization using the catalyst for a practical manufacturing method. We found that not only TBAI but also other inexpensive inorganic salts dramatically increased the catalytic activity. After optimization, the process for asymmetric hydrogenation of **7** was finalized as shown in Scheme 4, using **7·TsOH** as the substrate for the hydrogenation reaction. Addition of KBr (10 equiv to Ru) as a halide source was effective to enhance the reaction activity even at s/c 1000. Fortunately, we also found that crystallization from ethanol, after concentration of the asymmetric hydrogenation reaction mixture, gave **8** as a salt with *p*-toluenesulfonic acid in almost perfect enantioselectivity (99.7% ee) and 76% yield. Thus, we have developed an asymmetric process that is cost-effective, facile, and robust for scale-up manufacturing.

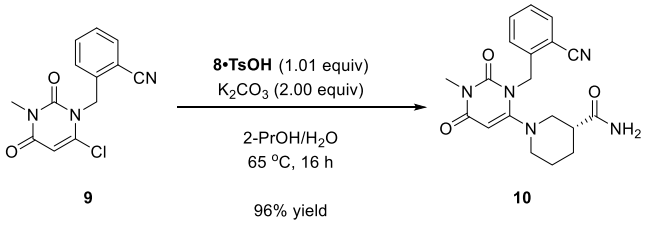
The asymmetric hydrogenation of **7·TsOH** has been scaled up without any issues. After further optimization, the reaction solvent was switched from methanol to 2-propanol for substrate stability, and the chiral catalyst was also changed from $Ru(CF_3CO_2)_2\{(S)$-phanephos$\}$ to $Ru(CF_3CO_2)_2\{(S)$-binap$\}$, bearing the inexpensive and widely used (*S*)-binap ligand, in thorough consideration of the impact on manufacturing cost. The designated asymmetric hydrogenation of **7·TsOH** (50.0 kg), under the conditions shown in Scheme 5, gave crude **8·TsOH** in full conversion with 70.1% ee. Subsequent recrystallization from ethanol finally provided 25.5 kg of **8·**

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

TsOH in 68% yield with 99.6% ee. The residual metal contents of Pd and Ru were <0.081 ppm and 3.6 ppm, respectively.

2-((6-Chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (10) Synthesis. Displacement of the chlorine on the 1,3-disubstituted chlorouracil **9** with **8·TsOH** was accomplished in the presence of potassium carbonate in aqueous 2-propanol at 65 °C for 16 h. To promote crystallization of 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (**10**), additional water was added to the reaction mixture. On a 12.0 kg scale of **9**, the manufacturing operation was implemented to give 15.3 kg of **10** without any scale-up issues (Scheme 6).

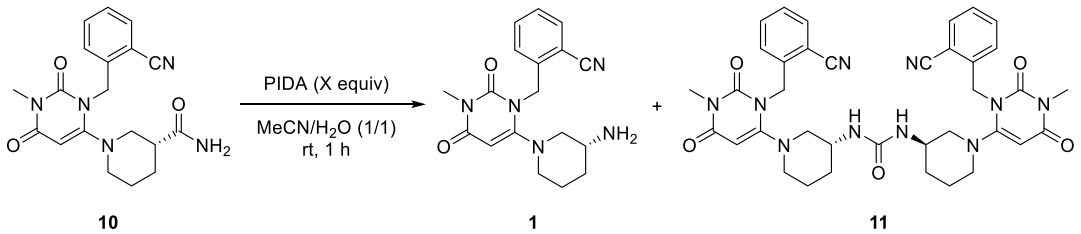
Scheme 6. Synthesis of 10



Hofmann Rearrangement of 10 and Salt Formation to 1. A variety of oxidizing agents have been known to promote Hofmann rearrangement, including NaOCl, NaOBr, and *N*-bromosuccinimide as principal examples.[6b,12] Recently, PIDA or iodobenzene bistrifluoroacetate as effective oxidizing agents have provided good reaction selectivity and high practicality.[13] We initially attempted using aq NaOCl, an inexpensive reagent, for Hofmann rearrangement of **10**. However, the resulting reaction mixture was complex, with side products such as the nonhydrolyzable symmetrical urea (**11**) being generated in the presence of diisopropylethylamine in MeCN/H_2O. The isolated yield of **1·BzOH** was 50% based on **10** with 97% assay, and these side products were difficult to remove by phase separation or crystallization. Next, we investigated the Hofmann rearrangement reaction condition using PIDA, to improve the reaction yield. We first studied the effect of the PIDA equivalence to **10** in MeCN/H_2O (1/1) at room temperature (Table 2). Increasing the amount of PIDA was effective to improve the reaction yield and to prevent the formation of **11** at room temperature. In order to reduce the amount of PIDA used as much as possible, for cost reduction, optimization of the equivalence of PIDA was required. Judging from the HPLC area % in Table 2, at least 1.3 equiv of PIDA was needed to complete the reaction (entry 4). Dimer formation was clearly suppressed by the excess amount of PIDA (entry 6).

The decomposition (hydration) of PIDA was considered as one of the major reasons for the necessity of excess PIDA, so the effect of additives was examined (Table 3). As a side note, controlling of urea (**11**) transformation under a small amount of PIDA was difficult, although we tried the various adding method of PIDA.[13a] The addition of inorganic bases showed that K_2CO_3 enhanced consumption of **10**, but a substantial amount of **11** was formed. Cooling the reaction to 0 °C had no effect to reduce **11** (entry 3). Although the addition of organic amines like Et_3N increased **11** formation, the addition of pyridine was effective for reaction completion, and the formation of **11** also slightly decreased (entries 6 and 7). It was interesting that PIDA was solubilized in the presence of pyridine, whereas it was hardly soluble in all the other solvent systems. Although the solubilization mechanism is still unclear, we considered that increasing the initial concentration of PIDA could facilitate the reaction to proceed. We suspected that the solubilizing effect would be obtained by a catalytic amount of pyridine, and indeed, no significant difference between the pyridine amounts was observed (entries 8−10). The reaction with a catalytic amount of pyridine also enabled us to change the solvent from MeCN to 2-propanol, a much more inexpensive and environmentally benign solvent (entry 11), while the reaction without pyridine did not go to completion, with 22% of **10** remaining, due to faster PIDA decomposition. Less **11** formation was observed in 2-propanol/H_2O than in MeCN/H_2O, with a little longer reaction time.

Table 2. Effect of the PIDA Amount in Hofmann Rearrangement of 10[a]

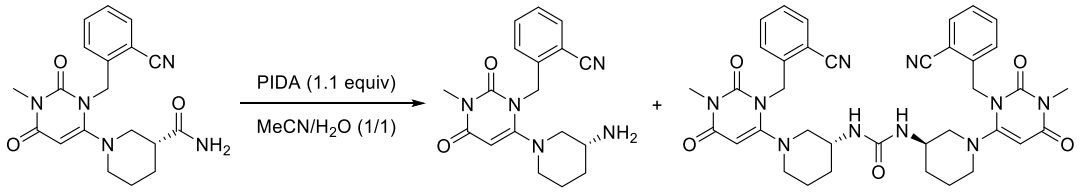


		HPLC (area %)[b,c]		
entry	PIDA (equiv)	10	1	11
1	1.0	5.5	84.8	6.6
2	1.1	2.0	89.4	5.7
3	1.2	0.5	92.3	5.2
4	1.3	0.1	94.5	3.6
5	1.5	0.2	95.1	2.4
6	2.0	0.1	96.1	1.1

[a]Unless otherwise stated, to a four-necked round bottomed flask, MeCN/H_2O (1/1) and **10** were charged. The solution was warmed to 50 °C for completely dissolving **10** and then cooled to 25 °C. PIDA was added to the solution, and then, the suspension was stirred for 1 h at 25 °C. [b]Any area contribution of iodosobenzene was ignored. [c]Determined by HPLC analysis, with condition: SHISEIDO MG II column (5 μm, 250 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 2.1 min (**1**), t_R: 2.5 min (**10**), and t_R: 6.0 min (**11**).

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Table 3. Effect of Bases for Hofmann Rearrangement of 10 by PIDA[a]

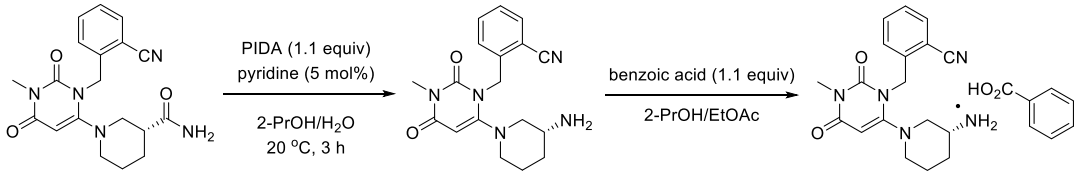


10 1 11

				HPLC (area %)[b,c]		
entry	base	temp. (°C)	time (h)	10	1	11
1		Rt	1	4.8	88.5	4.5
2	K_2CO_3 (3.0)	Rt	1	0.4	65.4	26.9
3	K_2CO_3 (3.0)	0	24	0.6	53.7	38.6
4	$NaHCO_3$ (2.0)	Rt	1	7.4	70.7	17.2
5	NaOH (2.0)	0 to rt	4	9.5	30.3	48.7
6	Et_3N (2.0)	Rt	1	2.9	52.7	36.1
7	pyridine (2.0)	Rt	1	1.0	92.9	3.6
8	pyridine (1.0)	Rt	1	0.2	95.1	3.0
9	pyridine (0.05)	Rt	1	0.1	95.6	3.1
10	pyridine (0.025)	Rt	1	0.1	95.5	3.2
11[d]	pyridine (0.025)	Rt	2	0.3	94.7	3.5

[a]Unless otherwise stated, to a four-necked round bottomed flask, MeCN/H_2O (1/1), base, and **10** were charged. PIDA was added to the solution, and then, the suspension was stirred. [b]Any area contribution of iodosobenzene was ignored. [c]Determined by HPLC analysis, with condition: SHISEIDO MG II column (5 μm, 250 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 2.1 min (**1**), t_R: 2.5 min (**10**), and t_R: 6.0 min (**11**). [d]2-propanol/H_2O = 1/1 was used as a reaction solvent.

Table 4. Hofmann Rearrangement and Benzoic Acid Salt Formation (50 g Scale)[a]



10 1 1·BzOH

	isolated yield (%)		HPLC (area %) of 1·BzOH[b,c]		residual metals (ppm)	
run	1	1·BzOH	1	11	Pd	Ru
1	89	93	99.79	0.07	0.026	3.1
2	87	92	99.88	0.03	<0.025	2.0
3	91	90	99.80	0.04	<0.026	2.2

[a]The operation procedure is described in the experimental section. [b]Any area contribution from benzoic acid was ignored. [c]Determined by HPLC analysis, with condition: SHISEIDO MG II column (5 μm, 250 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 2.1 min (**1**), t_R: 2.5 min (**10**), and t_R: 6.0 min (**11**).The optical yield of **1·BzOH** was 99.5% by chiral HPLC analysis, with condition: SUMICHIRAL OA-4600R column (5 μm, 250 × 4.6 mm), hexane/2-propano; /methanol/trifluoroacetic acid = 430/45/25/1, flow rate: 1.0 mL/min, oven temperature: 35 °C, detection: 275 nm (UV), t_R: 42.7 min (**enantiomer**), and t_R: 45.4 min (**1**).

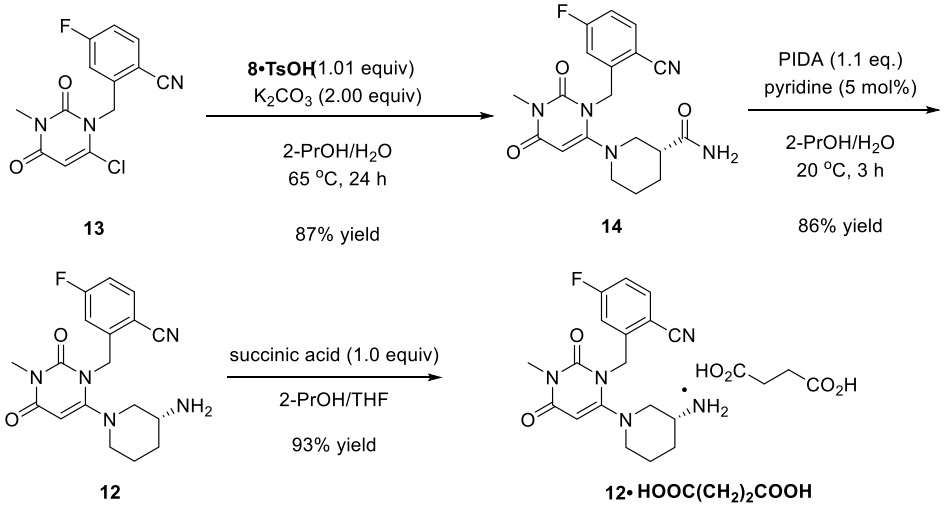
Isolation of 1 and Salt Formation to 1·BzOH. Although **1** had been isolated as a hydrochloride in the previous method, the salt exchange process from hydrochloride to benzoate before the final step was not operationally friendly. Here, **1** obtained *via* Hofmann rearrangement showed an improved HPLC profile and was able to be isolated as a crystalline-free base in around 90% yield from toluene/heptane. While the urea **11** was difficult to be removed by crystallization, due to its low solubility, **11** was found to be removable by back extraction of **1** in an acidic aqueous phase during work-up (for further details, see Experimental Section). After the work-up operation, **1** could be isolated in around 90% yield from toluene/heptane (10/15), which was adopted as the best crystallization solvent among the solvents screened. Additionally, we investigated an alternative solvent instead of ^{i}PrOAc, which was used as the extraction and crystallization solvent in the original route because of its significant effect on the manufacturing cost. An examination of **1·BzOH** salt formation using 2-propanol/EtOAc (1/1) showed that it gave high quality **1·BzOH** in good yield, which satisfied the established specification.

Next, the optimized reaction conditions from **10** to **1·BzOH** were applied to a 50 g scale synthesis, which was performed three times (Table 4).

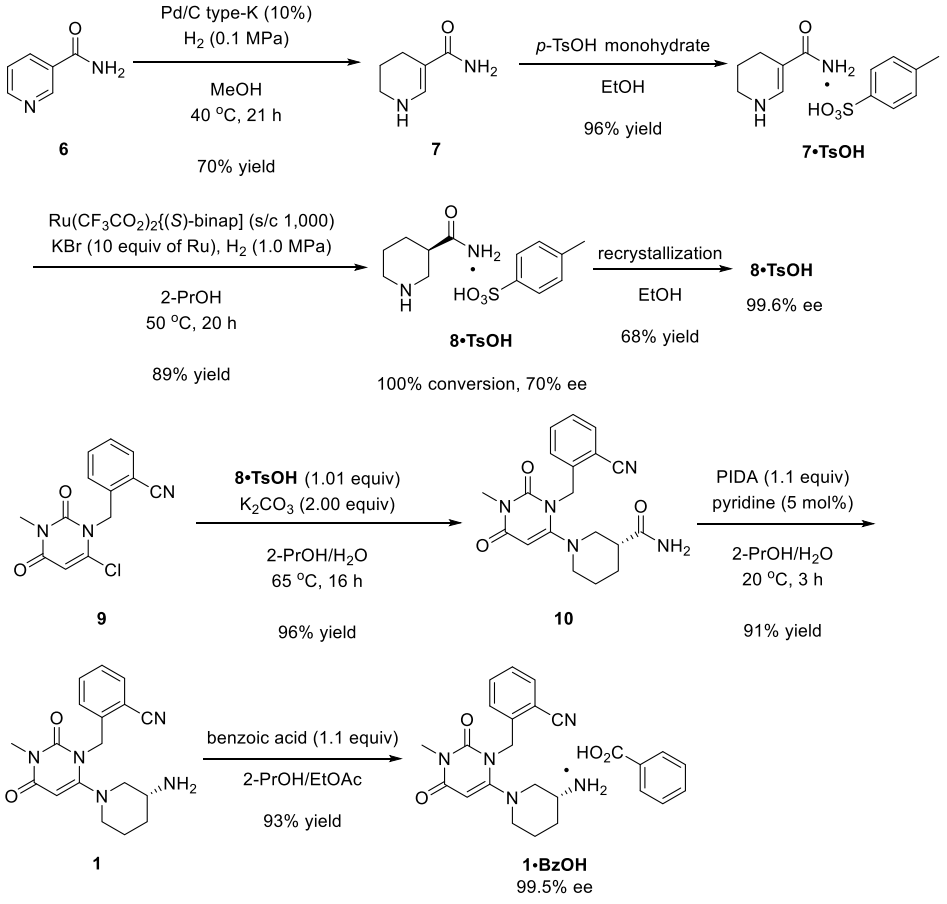
The three trials showed good reproducibility, and **1** and **1·BzOH** were obtained in 89 ± 2 and 92 ± 2%, respectively. As contamination by **11** in the first run was close to 0.1 area %, the amount of EtOAc for back extraction to remove **11** was increased from 5 to 10 vol. Hence, in the second and third runs, contamination by **11** could be reduced to less than 0.04 area %.

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Scheme 7. Synthesis of Trelagliptin (12) Succinate



Scheme 8. Overall Scheme of the Developed Synthetic Route to 1·BzOH



Thus, we could confirm the reproducibility of the economical reaction system on a 50 g scale, without any quality issues.

Application to Trelagliptin Succinate. Trelagliptin (**12**) succinate, a novel once-weekly oral DPP-4 inhibitor, was approved for the Japanese market in 2015 from Takeda Pharmaceutical Company.[1,14] As **12** has a similar molecular structure to **1** with only a single aromatic hydrogen atom being replaced by a fluorine, we investigated whether the developed method could be applied to the synthesis of **12** (Scheme 7).

The same conditions as for the synthesis of **1** were applied to the synthesis of **12**, and for the final succinate formation, the current conditions giving **12** were traced as well. Each reaction proceeded in good yield and gave the desired product in 70% yield in three steps from **13**.

CONCLUSIONS

In summary, the application of catalytic asymmetric hydrogenation to a key intermediate in the synthesis of alogliptin (**1**) resulted in the discovery of an enantioselective synthesis

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

pathway, as the key step (Scheme 8). The asymmetric hydrogenation of 1,4,5,6-tetrahydropyridine-3-carboxamide (**7**) and crystallization as the *p*-toluenesulfonate from ethanol gave (*R*)-nipecotamide (**8**) in >99% ee. With Ru-$(CF_3CO_2)_2$\{(*S*)-phanephos\}, it was possible to achieve an enantioselectivity of 88% ee in the reduction of **7·TsOH** to **8** in the presence of KBr at a catalyst loading of 1000:1 on a 66.7 g laboratory scale of **7·TsOH**, and then, 99.7% ee of **8·TsOH** was obtained by crystallization from ethanol, with 76% yield. The new procedure could be applied to a 50.0 kg scale **7·TsOH** manufactured using Ru$(CF_3CO_2)_2$\{(*S*)-binap\}, and 25.5 kg of **8·TsOH** was prepared in 68% yield.

Hofmann rearrangement of 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (**10**), prepared by the coupling of **8·TsOH** and the 1,3-disubstituted chlorouracil **9**, was successful using PIDA in the presence of a catalytic amount of pyridine. These new synthetic routes afforded **1** as crystals of the free base, and finally, **1** was converted to the benzoate salt in a 2-propanol/EtOAc system.

Moreover, the synthetic strategy was applicable for the preparation of trelagliptin (**12**), which has a similar molecular structure to **1**.

EXPERIMENTAL SECTION

General Remarks. All reagents and solvents were purchased commercially and used without further purification. HPLC analysis was performed on HITACHI 7400 instruments or SHIMADZU LC-10ADvp instruments. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, CD_3OD, or D_2O solutions at 500 and 126 MHz, respectively, using a Bruker Avance-III spectrometer for analysis of **7·TsOH**, **8·TsOH**, **10**, **1·BzOH**, **14**, and **12·HOOC$(CH_2)_2$COOH**. The IR spectrum was measured using a SHIMADZU IR Prestige-21. High-resolution mass spectrometry (HRMS) spectra were measured using a SHIMADZU LCMS-IT-TOF, and melting points were measured using a SIBATA B-545 apparatus. Specific rotations were measured using a JASCO P-1030.

Lab-Scale Synthesis of 1,4,5,6-Tetrahydropyridine-3-carboxamide (7) *p*-Toluenesulfonate. To a 1 L autoclave were added nicotinamide (50.00 g, 0.41 mol, 1.0 equiv) Pd/C type-K (5.00 g, 50%-wet) and methanol (500 mL). The atmosphere was purged with nitrogen gas seven times. Hydrogen was initially introduced into the autoclave at a pressure of 0.02 MPa, before being reduced to atmospheric pressure by carefully releasing the stop valve. After this procedure was repeated ten times, the hydrogen pressure was introduced at 0.1 MPa, and the solution was stirred at 40 °C for 21 h under 0.1 MPa of hydrogen pressure. The solution was cooled to room temperature, and hydrogen gas was then carefully vented. After removing Pd/C by filtration, the filtrates were evaporated to produce a white crystalline powder. The residue was diluted with methanol (100 mL), and the resulting suspension was aged at room temperature for 1 h. The solid was collected by filtration, and the cake was washed with methanol (50 mL) before being dried at 50 °C under vacuum to yield **7** as a colorless solid (36.20 g, 70% yield). To a four-necked round bottomed flask were charged the obtained powder (36.20 g), *p*-toluenesulfonic acid monohydrate (54.63 g, 0.29 mol, 1.00 equiv), and ethanol (290 mL, 8 vol). The suspension was aged at room temperature overnight and collected by filtration, and then, the cake was washed with a 1/4 v/v ethyl acetate-diisopropylether mixture and dried at 60 °C under vacuum to yield **7·TsOH** 0.85 ethanol solvate as a colorless solid (92.84 g, 96% yield, 100 area % HPLC purity). IR (KBr): 3379, 3296, 2978, 2949, 1665, 1609, 1437, 1410, 1177, 1123, and 1101 cm^{-1}. The product was detected as two isomers in the ratio of 87 (major):13 (minor) by NMR measurements. ^{1}H NMR (500 MHz, D_2O): δ 7.62 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 5.09 (s, 0.13H), 4.79 (s, 0.87H), 3.57 (q, J = 6.5 Hz, 0.85 × 2H), 3.24−3.40 (m, 1H), 2.91−3.11 (m, 1H), 2.31 (s, 3H), 1.76−2.08 (m, 2H), 1.53−1.71 (m, 2H), 1.10 (t, J = 6.5 Hz, 0.85 × 3H). ^{13}C NMR (126 MHz, D_2O): δ 176.1 (0.13C), 175.9 (0.87C), 142.5 (1C), 139.9 (1C), 129.6 (1C), 125.6 (1C), 80.0 (0.87C), 78.1 (0.13C), 57.6 (0.87C), 47.5 (0.13C), 47.4 (0.13C), 47.2 (0.13C), 43.2 (1C), 40.7 (0.13C), 25.6 (0.87C), 22.0 (0.13C), 20.7 (1C), 20.5 (0.87C), 19.1 (0.13C), 17.0 (0.87C). HRMS (m/z, ESI): calcd 127.0866 for $C_6H_{10}N_2O$ $(M + H)^+$; found, 127.0873; calcd 171.0121 for $C_7H_8O_3S$ $(M - H)^-$; found, 171.0124. HPLC: SHISEIDO CD-Ph column (5 μm, 250 × 4.6 mm), MeCN/aq KPF_6 (0.10 M) 5/95, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 200 nm (UV), t_R: 8.5 min (*p*-toluenesulfonic acid), t_R: 12.0 min (**7**), t_R: 19.0 min (**6**).

Lab-Scale Synthesis of (*R*)-Nipecotamide (8) *p*-Toluenesulfonate. To a 1 L autoclave were added Ru-$(CF_3CO_2)_2$\{(*S*)-phanephos\} (0.1785 g, 0.198 mmol, 0.001 equiv = s/c 1,000), potassium bromide (0.2350 g, 1.98 mmol, 0.01 equiv), and **7·TsOH** 0.85 ethanol solvate (66.67 g, 197.5 mmol, 1.00 equiv). The atmosphere was evacuated and filled with argon gas seven times. Dehydrated methanol (500 mL) was added to the autoclave by the argon feed cannula. The mixture was stirred at room temperature for 5 min, and hydrogen was initially introduced into the autoclave at a pressure of 0.1 MPa, before being reduced to atmospheric pressure by carefully releasing the stop valve. After this procedure was repeated ten times, the hydrogen pressure was introduced at 1.0 MPa, and the solution was stirred at 50 °C for 15 h. The solution was cooled to room temperature, and hydrogen gas was then carefully vented. After evaporation of the solvent, the residue was evaporated to afford a pale-green solid. The residue was dissolved with ethanol (201 mL) at 75 °C, and the insolubles were removed by filtration. The filtrates were evaporated to dryness. The residue was diluted with ethanol (201 mL) and stirred at 80 °C for 1 h. The seed crystal of **8·TsOH** was inoculated to the solution. The resulting suspension was cooled to room temperature and aged for 3 h. The solid was collected by filtration, and the cake was washed with ethanol (142 mL) before being dried at 60 °C under vacuum to yield **8·TsOH** as a colorless solid (44.99 g, 76% yield, 99.7% ee as benzylated **8**). $[\alpha]_D^{25}$—0.3° (c = 0.996, methanol); IR (KBr): 3400−3300, 3159, 2950−2800, 1670, 1435, and 1171 cm^{-1}. ^{1}H NMR (500 MHz, D_2O): δ 7.73 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 3.37−3.45 (m, 1H), 3.28−3.36 (m, 1H), 3.16−3.24 (m, 1H), 3.05−3.14 (m, 1H), 2.82−2.92 (m, 1H), 2.43 (s, 3H), 2.82−2.92 (m, 1H), 2.43 (s, 3H), 2.03−2.14 (m, 1H), 1.92−2.03 (m, 1H), 1.74−1.89 (m, 2H). ^{13}C NMR (126 MHz, D_2O): δ 177.4, 142.6, 139.9, 129.6, 125.6, 44.9, 44.1, 38.5, 25.6, 20.7, 20.6. Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33; S, 10.68. Found: C, 52.19; H, 6.79; N, 9.31; S, 10.57. HRMS (m/z, ESI): calcd 129.1022 for $C_6H_{12}N_2O$ $(M + H)^+$; found, 129.1046; calcd 171.0121 for $C_7H_8O_3S$ $(M - H)^-$; found, 171.0130. HPLC: CHIRALPAK IC column (5 μm, 250 × 4.6 mm), MeCN/aq H_3PO_4 (0.020 M) 3/7, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 200 nm (UV). The sample was converted to the benzylated form; t_R: 13.1 min (*N*-benzylated *ent*-**8**), t_R: 17.2 min (*N*-benzylated **8**).

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Lab-Scale Synthesis of 2-((6-Chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-benzonitrile (10). To a 1 L four-necked round bottomed flask were charged 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (**9**) (27.54 g, 99.90 mmol, 1.0 equiv), **8·TsOH** (30.00 g, 99.98 mmol, 1.0 equiv), potassium carbonate (27.61 g, 199.8 mmol, 2.00 equiv), 2-PrOH (210 mL), and water (3 mL). This suspension was heated to 70 °C and stirred for 18 h. The reaction mixture was cooled to 25 °C and evaporated under reduced pressure. The resulting suspension was stirred at room temperature for 2 h. The solid was collected by filtration, and the cake was washed with water (90 mL) and dried at 60 °C under vacuum to yield **10** as a colorless solid (34.13 g, 93% yield, 95.9 area % HPLC purity). $[\alpha]_D^{25}$ + 21.4° (*c* = 0.977, methanol); IR (KBr): 3387, 3319, 3202, 2941, 2853, 2226, 1690, 1676, and 1628 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.51 (td, *J* = 8.0, 1.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 5.73 (bs, 1H), 5.67 (bs, 1H), 5.34 (s, 1H), 5.32 (d, *J* = 16.0 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 3.25 (s, 3H), 3.12−3.20 (dm, 1H), 2.88 (d, *J* = 11.5 Hz, 1H), 2.72 (t, *J* = 11.5 Hz, 1H), 2.55 (t, *J* = 11.5 Hz, 1H), 2.47 (tt, *J* = 11.5, 3.5 Hz, 1H), 1.91 (dd, *J* = 13.0, 3.5 Hz, 1H), 1.70 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.57 (qd, *J* = 13.0, 3.5 Hz, 1H), 1.46 (qt, *J* = 13.0, 4.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8, 163.2, 159.8, 153.0, 141.0, 133.6, 133.3, 128.2, 127.2, 117.7, 110.7, 91.3, 54.0, 51.9, 46.4, 42.5, 28.2, 27.3, 24.3. HRMS (*m*/*z*, ESI): calcd 368.1717 for $C_{19}H_{21}N_5O_3$ $(M + H)^+$; found, 368.01731. HPLC: YMC-Pack ODS-A302 column (5 μm, 150 × 4.6 mm), MeCN/aq H_3PO_4 (0.020 M) 3/7, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 225 nm (UV), t_R: 8.7 min (**10**), t_R: 25.1 min (**9**).

Lab-Scale Synthesis of Alogliptin (1). To a 2 L four-necked round bottomed flask, H_2O/2-PrOH (1/1, 1.5 L), pyridine (550 μL, 6.9 mmol, 0.05 equiv), and **10** (50.0 g, 136 mmol, 1.00 equiv) were charged. PIDA (48.2 g, 150 mmol, 1.1 equiv) was added to the solution, and then, the suspension was stirred for 3 h at 20 °C. The solvents (750 ± 50 mL) were evaporated *in vacuo* at 40 °C, and then, EtOAc (500 mL) was added, and the aqueous layer was separated. The aqueous layer was washed by EtOAc (500 mL) and treated with K_2CO_3 (400 g) at 0−15 °C. The organic products were extracted with toluene (100 mL) and 2-PrOH (150 mL), followed by rinsing with saturated aq NaCl (50 mL). After evaporation of the organic solvents, toluene (150 mL) was added and evaporated for solvent substitution. **1** was crystallized from toluene (100 mL) and heptane (150 mL, dropwise for 1 h) as a yellowish white crystalline solid (40.3 g, 87.2% yield, 99.31 area % HPLC purity). HPLC: YMC-Pack ODS-A302 column (5 μm, 150 × 4.6 mm), MeCN/aq H_3PO_4 (0.020 M) 3/7, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 225 nm (UV), t_R: 3.2 min (**1**), t_R: 8.7 min (**10**).

Lab-Scale Synthesis of Alogliptin (1) Benzoate. **1** (35 g, 103 mmol, 1.00 equiv) was dissolved in hot IPA (140 mL, 60 °C) then filtered through a membrane filter to a 1 L four-necked round bottomed flask. Benzoic acid (13.8 g, 113 mmol, 1.1 equiv) in EtOAc (140 mL) was added dropwise to the solution for 1 h at 60 °C. The crystals were aged for 19 h at room temperature. The resulting solid material was filtered and dried *in vacuo* at 50 °C to give a slightly yellowish crystalline solid (43.9 g, 92% yield, 99.79 area % HPLC purity). mp 184.0−186.1 °C; IR (KBr): 3082, 2976, 2961, 2860, 2230, 1695, 1609, 1591, 1445 and 1362 cm^{-1}. ^1H NMR (500 MHz, D_2O): δ 7.76 (d, *J* = 7.0 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.28−7.42 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 1H), 5.43 (s, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 3.25−3.45 (m, 2H), 3.03 (s, 3H), 2.77−2.96 (m, 2H), 2.57−2.77 (m, 1H), 1.95−2.08 (m, 1H), 1.68−1.80 (m, 1H), 1.47−1.63 (m, 2H). ^{13}C NMR (126 MHz, D_2O) Peaks of ethanol were detected: δ 175.3, 165.4, 160.4, 152.9, 140.1, 47.1, 136.3, 133.3, 133.7, 131.1, 128.9, 128.3, 128.2, 128.0, 118.0, 109.4, 90.2, 57.5, 52.2, 51.7, 46.9, 27.9, 27.2, 21.2, 16.9. HRMS (*m*/*z*, ESI): calcd 340.1768 for $C_{19}H_{21}N_5O_3$ $(M + H)^+$; found, 340.1769. HPLC: SHISEIDO MG II column (5 μm, 150 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 2.1 min (**1**), t_R: 2.5 min (**10**), t_R: 6.0 min (**11**). Chiral HPLC: SUMICHIRAL OA-4600R column (5 μm, 250 × 4.6 mm), hexane/2-propano; /methanol/trifluoroacetic acid = 430/45/25/1, flow rate: 1.0 mL/min, oven temperature: 35 °C, detection: 275 nm (UV), t_R: 42.7 min (**enantiomer**), t_R: 45.4 min (**1**).

Lab-Scale Synthesis of (*R*)-1-(3-(2-Cyano-5-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidine-3-carboxamide (14). To a 50 mL round bottomed flask equipped with a reflux condenser were added H_2O/2-PrOH (8/3, 27.5 mL), **8·TsOH** (5.0 g, 16.6 mmol, 0.99 equiv), and 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-4-fluorobenzonitrile (**13**) (4.9 g, 16.8 mmol, 1.00 equiv). K_2CO_3 (4.6 g, 33.2 mmol, 1.98 equiv) was added, and then, the reaction was heated to 65 °C and stirred for 24 h. During the reaction, the resulting amide started to crystallize. After the addition of H_2O (30 mL), the reaction mixture was cooled to 0 °C, stirred for 1 h, and then filtered. The crystals obtained were washed with H_2O (10 mL) and dried *in vacuo* at 45 °C to give a reddish white crystalline solid (5.6 g, 87% yield, 97.6 area % HPLC purity). ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 8.7 Hz, 5.2 Hz, 1H), 7.10 (td, *J* = 8.0 Hz, 2.5 Hz, 1H), 6.90 (dd, *J* = 9.1 Hz, 2.5 Hz, 1H), 5.66 (brs, 1H), 5.48 (brs, 1H), 5.42 (s, 1H), 5.38 (d, *J* = 16.08 Hz, 1H), 5.17 (d, *J* = 16.4 Hz,1H), 3.34 (s, 3H), 3.14−3.28 (m, 1H), 2.94 (d, *J* = 12.0 Hz, 1H), 2.82 (t, *J* = 10.6 Hz, 1H), 2.64 (t, *J* = 10.9 Hz,1H), 2.49−2.59 (m, 1H), 1.92−2.07 (m, 1H), 1.80 (m, 1H), 1.62−1.72 (m, 1H), 1.45−1.60 (m, 1H). HPLC: SHISEIDO MG II column (5 μm, 150 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 2.7 min (**14**).

Lab-Scale Synthesis of Trelagliptin (12). To a 100 mL four-necked round bottomed flask, H_2O/2-PrOH (1/1, 60 mL), pyridine (21.4 μL, 0.26 mmol, 0.05 equiv), and **14** (2.0.0 g, 5.2 mmol) were charged. PIDA (1.84 g, 5.7 mmol, 1.10 equiv) was added to the solution, and then, the suspension was stirred for 3 h at 20 °C. The solvents (*ca.* 40 mL) were evaporated *in vacuo* at 30 °C, and then, EtOAc (20 mL) was added, and the aqueous layer was separated. The aqueous layer was washed with EtOAc (20 mL) and treated with K_2CO_3 (16 g) at 0−15 °C. The organic products were extracted with toluene (6 mL) and 2-PrOH (6 mL), followed by rinsing with saturated aq NaCl (10 mL). After evaporation of the organic solvents, toluene (6 mL) was added and evaporated for solvent substitution. Product **12** was crystallized from toluene (6 mL) and heptane (6 mL, dropwise for 1 h) at 0 °C as a white crystalline solid (1.6 g, 86% yield, 99.2 area % HPLC purity). ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 8.5 Hz, 5.4 Hz, 1H), 7.09 (td, *J* = 8.0 Hz, 2.5 Hz, 1H), 6.86 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 5.39 (s, 1H), 5.23−5.32 (m, 2H), 3.32 (s, 3H), 2.99−3.05 (m, 1H), 2.87−2.98 (m, 2H), 2.61 (m, 1H), 2.41 (m,1H), 1.95 (dd, *J* = 12.8 Hz, 3.9 Hz, 1H), 1.72−1.83 (m, 1H), 1.56−1.67 (m, 1H), 1.30 (brs, 2H), 1.23 (d,

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

J = 11.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.9, 159.5, 152.7, 144.6, 135.5, 135.4, 116.4, 115.8, 115.6, 114.7, 114.6, 90.8, 59.7, 51.9, 46.1, 33.4, 28.0. HPLC: SHISEIDO MG II column (5 μm, 150 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 1.4 min (**12**), t_R: 2.7 min (**14**).

Lab-Scale Synthesis of Trelagliptin (12) Succinate. Crystalline **12** (1.0 g, 2.8 mmol, 1.00 equiv) was dissolved in hot THF (4.5 mL) with 2 drops of water, and the solution was filtered through a membrane filter. Then, the solution was slowly added to an already filtered succinic acid (331 mg, 2.8 mmol) solution in THF (4 mL) and 2-PrOH (2.5 mL) at 65 °C. Crystals formed and were aged at 65 °C for 30 min; then, the suspension was cooled to room temperature. After stirring for 16 h, the suspension was cooled to 0−5 °C and stirred for a further 2 h. The crystals were filtered and dried *in vacuo* at 45 °C to give a white crystalline solid (1.2 g, 93% yield, 99.8 area % HPLC purity). The ^{1}H NMR spectrum was identical with the reported data.[14] ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.95 (dd, J = 8.7 Hz, 5.5 Hz, 1H), 7.35 (td, J = 8.5 Hz, 2.5 Hz, 1H), 7.17 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 5.38 (s, 1H), 5.20 (d, J = 16.4 Hz, 1H), 5.12 (d, J = 16.1 Hz, 1H), 3.14 (m, 1H), 3.09 (s, 3H), 3.08 (m, 1H), 3.00−3.07 (m, 1H), 2.91 (d, J = 11.4 Hz, 1H), 2.54−2.77 (m, 2H), 1.66−1.97 (m, 2H), 1.42−1.57 (m, 1H), 1.35 (d, J = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 175.2, 166.1, 164.1, 162.7, 159.7, 152.3, 145.8, 136.53, 136.45, 117.1, 115.7, 106.9, 90.3, 55.8, 51.7, 47.0, 46.3, 31.6, 27.9. HPLC: SHISEIDO MG II column (5 μm, 150 × 4.6 mm), 0.02 M aq H_3PO_4/MeCN = 6/4, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 278 nm (UV), t_R: 1.4 min (**12**), t_R: 2.7 min (**14**).

Manufacturing for Scale-Up Study. *Kilogram-Scale Synthesis of 1,4,5,6-Tetrahydropyridine-3-carboxamide (**7**) p-Toluenesulfonate.* A nitrogen-substituted 1,500 L pressure reactor was charged with nicotinamide (**6**) (70.0 kg, 0.573 kmol, 1.00 equiv), Pd/C type-K (7.0 kg, 50% wet), and methanol (700 L, 10 vol). The reactor was pressurized with hydrogen (0.07 MPa) and vented nine times. The hydrogen pressure was set to 0.08 MPa, and heating was started. After a reaction temperature of 37 °C was reached, the pressure was adjusted to 0.10 MPa. The reaction mixture was stirred with the hydrogen pressure maintained within the range of 0.09−0.10 MPa at 37−43 °C for 33 h. The reactor was cooled below 40 °C, and the hydrogen was carefully vented. The reactor was pressurized with nitrogen (0.02 MPa) and vented four times. The reaction mixture was heated to 55 °C and stirred at 55 °C for 1 h. Pd/C was removed by nitrogen-pressurized filtration at 50−57 °C with methanol rinsing (70 L). The filtrates were concentrated under reduced pressure to about 210 L (3 vol). The resulting slurry was cooled to 5 °C and aged at 5 °C for 2 h. The solid was collected by filtration, and the cake was washed with cool methanol (42 L, 0.6 vol). A 1,200 L reactor was charged with the wet-collected powder and ethanol (420 L, 6 vol). *p*-Toluenesulfonic acid (87.2 kg, 0.458 kmol, 0.80 equiv) was added to the reactor at 26 °C, and then, a seed crystal of **7·TsOH** (70 g) was inoculated. The resulting suspension was aged at 25 °C for 3 h before being filtered, and then, the cake was washed with ethanol (140 L, 2 vol) and dried at 60 °C under vacuum to yield **7·TsOH** 0.85 ethanol solvate as a colorless solid (116.3 kg, 60% yield). HPLC analysis of a sample matched that of one from the laboratory-scale synthesis.

*Kilogram-Scale Synthesis of (R)-Nipecotamide (**8**) p-Toluenesulfonate.* A 500 L pressure reactor was charged with **7·TsOH** 0.85 ethanol solvate (50.0 kg, 0.148 kmol, 1.00 equiv), potassium bromide (176.20 g, 1.481 mol, 0.01 equiv), and $Ru(CF_3CO_2)_2$\{(*S*)-binap\} (140.60 g, 1.480 mol, 0.01 equiv, s/c 1,000). The reactor was evacuated to −0.09 MPa and then filled with nitrogen to 0.10 MPa. This operation was repeated seven times. To the reactor was added anhydrous 2-propanol (370 L, 7.4 vol) by nitrogen gas feed. The reactor was stirred at 15−21 °C for 2 h. Then, the reactor was pressurized with nitrogen (0.60 MPa), vented three times, pressurized with hydrogen (0.10 MPa), and vented nine times. The hydrogen pressure was set to 0.70 MPa, and heating was started. After a reaction temperature of 45 °C was reached, the pressure was adjusted to 0.80 MPa. The reaction mixture was stirred with the hydrogen pressure maintained within the range of 0.79−0.81 MPa at 46−50 °C (set point 50 °C) for 20 h. The reactor was cooled below 10 °C, and the hydrogen was carefully vented. The reactor was pressurized with nitrogen (0.05 MPa) and vented four times. Then, 2-propanol (25 L, 0.5 vol) was added, and the mixture was stirred at 8−9 °C for 3 h. The solid was collected by filtration, and the cake was washed with 2-propanol (75 L, 1.5 vol) before being dried at 60 °C under vacuum to yield crude **8·TsOH** (39.7 g, 89% yield, 70.1% ee). To a reactor were added crude **8·TsOH** and ethanol (302 L, 8 vol). The suspension was heated to around 75 °C to dissolve the solid and then stirred at 73 °C for 1 h. The resulting solution was cooled to 60 °C before adding a seed crystal of **8·TsOH** (30 g). The resulting suspension was cooled to 25 °C over 2 h and aged at 25 °C for 3 h. The solid was collected by filtration, and then, the cake was washed with 2-propanol (57 L, 1.5 vol) and dried at 50 °C under vacuum to yield **8·TsOH** as a colorless solid (25.5 kg, 68% yield, 99.7% ee). HPLC analysis of a sample matched that of one from the laboratory-scale synthesis.

*Kilogram-Scale Synthesis of 2-((6-Chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)benzonitrile (**10**).* To a reactor were charged 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)benzonitrile (**9**) (12.0 kg, 43.53 mol, 1.00 equiv), **8·TsOH** (13.2 kg, 43.95 mol, 1.01 equiv), potassium carbonate (12.1 kg, 87.55 mol, 2.01 equiv), 2-PrOH (14.4 L, 1.2 vol), and water (58.6 L, 4.8 vol). This suspension was heated to 65 °C and stirred for 18 h. To the reaction mixture was added water (79.2 L, 6.6 vol), and then, it was gradually cooled to 5 °C. The resulting suspension was stirred at 5 °C for 3 h. The solid was collected by filtration, and the cake was washed with water (48.0 L, 4.0 vol) and dried at 60 °C under vacuum to yield **10** as a pale-yellow solid (15.3 kg, 96% yield, 99.4 area % HPLC purity). HPLC analysis of a sample matched that of one from the laboratory-scale synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00544.

General analytical methods and available copies of HPLC chromatograms and ^{1}H NMR and ^{13}C NMR for compounds **7·TsOH**, **8·TsOH**, **10**, **1·BzOH**, **14**, and **12·HOOC(CH$_2$)$_2$COOH** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Masatoshi Yamada − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan;* orcid.org/0000-0002-8390-6021; Email: masatoshi.yamada@spera-pharma.co.jp

https://dx.doi.org/10.1021/acs.oprd.0c00544
Org. Process Res. Dev. 2021, 25, 327−336

Authors

Sayuri Hirano − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Ryoji Tsuruoka − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan;* orcid.org/0000-0003-3748-9172

Masahiro Takasuga − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Kenichi Uno − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Kotaro Yamaguchi − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Mitsuhisa Yamano − *Process Chemistry, Pharmaceutical Sciences, Takeda Pharmaceutical Company Limited, Osaka, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.0c00544

Notes

The authors declare the following competing financial interest(s): The research described was totally funded by TAKEDA Pharmaceutical Company Limited.

■ ACKNOWLEDGMENTS

We thank our industrial partners Hamari Chemicals, Ltd for the manufacturing operation of the asymmetric hydrogenation and FUJIFILM Wako Pure Chemical Corporation for catalyst preparation. Also, we thank our TAKEDA colleague Kenji Kuroda and SPERA colleagues Hideya Mizufune, Toshihiko Fujitani, David Cork, Koichiro Fukuoka, and Koji Mukai for their helpful discussions regarding this project.

■ REFERENCES

(1) Feng, J.; Gwaltny, S. L.; Stafford, J. A.; Zhang, Z. Dipeptidyl Peptidase Inhibitors. WO 2005095381 A1, 13 Oct 2005.

(2) Feng, J.; Gwaltny, S. L.; Stafford, J. A.; Zhang, Z.; Elder, B. J.; Isbester, P. K.; Palmer, G. J.; Salsbury, J. S.; Ulysse, L. Dipeptidyl Peptidase Inhibitors. WO 2007035629 A2, 29 March 2007.

(3) Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J. A.; Kaldor, S. W.; Kassel, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney, S. L. Discover of Alogliptin: A Potent, Selective, Bioavailable, and Efficacious Inhibitor of Dipeptidyl Peptidase IV. *J. Med. Chem.* **2007**, *50*, 2297−2300.

(4) Fujita, H.; Taniai, H.; Murayama, H.; Ohshiro, H.; Hayashi, H.; Sato, S.; Kikuchi, N.; Komatsu, T.; Komatsu, K.; Komatsu, K.; Narita, T.; Yamada, Y. DPP-4 inhibition with alogliptin on top of angiotensin II type 1 receptor blockade ameliorates albuminuria via up-regulation of SDF-1α in type 2 diabetic patients with incipient nephropathy. *Endocr. J.* **2014**, *61*, 159−166.

(5) https://www.takeda.com/en-ca/newsroom/news-releases/2015/new-takeda-type-2-diabetes-treatments-nesina-alogliptin-and-kazano-alogliptin-and-metformin-hydrochloride-now-available-for-quebec-patients/ (accessed before September 2020).

(6) (a) Samuel, H. J.; Meek, G. A. Method for Producing 3-Aminopiperidine Diastereomer. WO 2007075630 A1, 5 July 2007. (b) Mori, K.; Nishiyama, A.; Nojiri, M.; Taoka, N. Method for Producing Optically Active 3-Aminopiperidine or salt thereof. WO 2008102720 A1, 28 Aug 2008. (c) Wallace, M. B.; Cody, J.; Fornicola, R.; Garcia-Rubio, S.; Kisanga, P. B.; Reeve, M. M.; Wilson, C. Preparation of (R)-3-aminopiperidine dihydrochloride. WO 2007112368 A1, 4 Oct 2007.

(7) Yamada, M.; Hirano, S.; Tsuruoka, R.; Yamano, M. Process for Producing Heterocyclic Compound. WO 2015137496 A1, 17 Sep 2015.

(8) (a) Quan, P. M.; Quin, L. D. 1,4,5,6-Tetrahydropyridines from Catalytic Reduction of Nicotinoyl Derivatives and Their Ring Opening with Hydrazine. *J. Org. Chem.* **1966**, *31*, 2487−2490. (b) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. Tetrahydropyridines. *J. Org. Chem.* **1968**, *33*, 747−753.

(9) (a) Fuchs, R.; Roduit, J.-P. Process for the Preparation of Optically Active Piperidine 2-Carboxylic Acid Derivatives. U.S.Patent 5,886,181 A, 3 March 1999. (b) Lei, A.; Chen, M.; He, M.; Zhang, X. Asymmetric Hydrogenation of Pyridines: Enantioselective Synthesis of Nipecotic Acid Derivatives. *Eur. J. Org. Chem.* **2006**, *2006*, 4343−4347.

(10) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. Convenient Preparation of Binap-Ruthenium (II) Complexes Catalyzing Asymmetric Hydrogenation of Functionalized Ketones. *Tetrahedron Lett.* **1991**, *32*, 4163−4166.

(11) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. [2.2]Phanephos-Ruthenium(II) Complexes: Highly Active Asymmetric Catalysts for the Hydrogenation of β-Ketoesters. *Tetrahedron Lett.* **1998**, *39*, 4441−4444.

(12) (a) Hofmann, A. W. Ueber die Einwirkung des Broms in alkalischer Lösuug auf Amide. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725−2736. (b) Chai, Y.; Wan, Z.-L.; Wang, B.; Guo, H.-Y.; Liu, M.-L. Synthesis and in vitro antibacterial activity of 7-(4-alkoxyimino-3-amino-3-methylpiperidin-1-yl)fluoroquinolone derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 4063−4069. (c) Ewing, W. R.; Zhu, Y.; Sun, C.; Huang, Y.; Karatholuvhu, M. S. Diaminocyclohexane Compounds and Uses Thereof. WO 2013012829 A1, 24 Jan 2013.

(13) (a) Abrecht, S.; Adam, J.-M.; Bromberger, U.; Diodone, R.; Fettes, A.; Fischer, R.; Goeckel, V.; Hildbrand, S.; Moine, G.; Weber, M. An Efficient Process for the Manufacture of Carmegliptin. *Org. Process Res. Dev.* **2011**, *15*, 503−514. (b) Taylor, G. M.; Baker, S. J.; Gedney, A.; Pearson, D. J.; Sibley, G. E. M. On the Ritter Reaction of Cyclic Hydroxyamines: Synthesis of Conformationally-Restricted Reduced Amide Dipeptide Isosteres. *Tetrahedron Lett.* **1996**, *37*, 1297−1300. (c) Mercado-Martin, E. V.; Garcia, R. P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R. *Nature* **2014**, *509*, 318−324.

(14) Zhang, Z.; Wallace, M. B.; Feng, J.; Stafford, J. A.; Skene, R. J.; Shi, L.; Lee, B.; Aertgeerts, K.; Jennings, A.; Xu, R.; Kassel, D. B.; Kaldor, S. W.; Navre, M.; Webb, D. R.; Gwaltney, S. L. Design and Synthesis of Pyrimidinone and Pyrimidinedione Inhibitors of Dipeptidyl Peptidase IV. *J. Med. Chem.* **2011**, *54*, 510−524.