Organic Process Research & Development

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The Development of an Asymmetric Hydrogenation Process for the Preparation of Solifenacin

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Supporting Information

ABSTRACT: The successful development of a catalytic imine asymmetric hydrogenation process for the reduction of the hydrochloride salt of 1-phenyl-3,4-dihydroisoquinoline to 1-(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline is described. This represents a novel approach to the key intermediate in preparing the urinary antispasmodic drug solifenacin, (1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1*H*)-isoquinoline carboxylate. Suitable reaction conditions were identified through an extensive screen of catalysts and combination of solvents and additives. The best reaction conditions: $[Ir(COD)Cl]_2$-(*S*)-P-Phos, molar substrate to catalyst ratio (S/C) of >1000/1, THF, 1−2 equiv of H_3PO_4, 60 °C, 20 bar H_2, were reproduced on a 200 g scale (95% isolated yield, 98% ee and >99% HPLC product purity).

INTRODUCTION

(1*S*)-(3*R*)-1-Azabicyclo[2.2.2]oct-3-yl-3,4-dihydro-1-phenyl-2(1*H*)-isoquinoline carboxylate (**1**), solifenacin, is a urinary antispasmodic.[1] The succinate salt of **1**, commercialized as Vesicare, is FDA approved for the treatment of overactive bladder. Several synthetic strategies have been devised, by both academic[2] and industrial research groups.[3,4] The strategy used on industrial scale for the synthesis of solifenacin involves a Bischler−Napieralski cyclization followed by achiral reduction of the resulting imine **2** (Scheme 1). Commonly, diastereomeric resolution of the tartrate salt of racemic **3** provides (*S*)-**3**,[5] which then reacts with a (halo)alkyl haloformate to yield the desired **1**. A variation of the reaction describes the use of an alkali metal salt of (*R*)-3-quinuclidinol in reaction with the (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate intermediate.[4d] Alternatively, the diastereoisomers of **1** can be resolved by chromatography.[4e]

The common feature of most of these approaches is the use of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **3** as the key intermediate. It is widely accepted that asymmetric catalysis in industrial processes can provide superior yield and reduce the waste streams during the synthesis of pharmaceutical intermediates. In this contribution we report the synthesis of enantiomerically enriched (*S*)-**3** from the hydrochloride salt of its imine precursor, **2·HCl**, using iridium-catalyzed asymmetric hydrogenation (Scheme 2).[4g]

RESULTS AND DISCUSSION

The catalytic asymmetric reduction of prochiral C=N bonds has been widely investigated, and the number of imines have been reduced with high activity and selectivity using Ir, Rh, Pd, and Ru chiral catalysts under a variety of reaction conditions.[6] Cyclic imines are of particular interest. Contrary to 1-alkyl-3,4-dihydroisoquinolines (alkyl = benzyl, linear alkyl), for which a number of efficient asymmetric reduction methodologies have been reported,[7,8] 1-aryl-3,4-dihydroisoquinolines are particularly challenging substrates. Only a very limited number of transfer hydrogenation[9] and hydrogenation[10] catalysts have been reported to be successful.

1. Substrate Preparation. Imine **2·HCl** was prepared according to published procedures.[4g,11] The research work reported here focused on the direct asymmetric hydrogenation of the hydrochloride salt **2·HCl**, which could be conveniently prepared and purified prior to the hydrogenation step. Attempts to hydrogenate the crude starting material as free base **2** with or without purification gave lower activity (see Supporting Information).

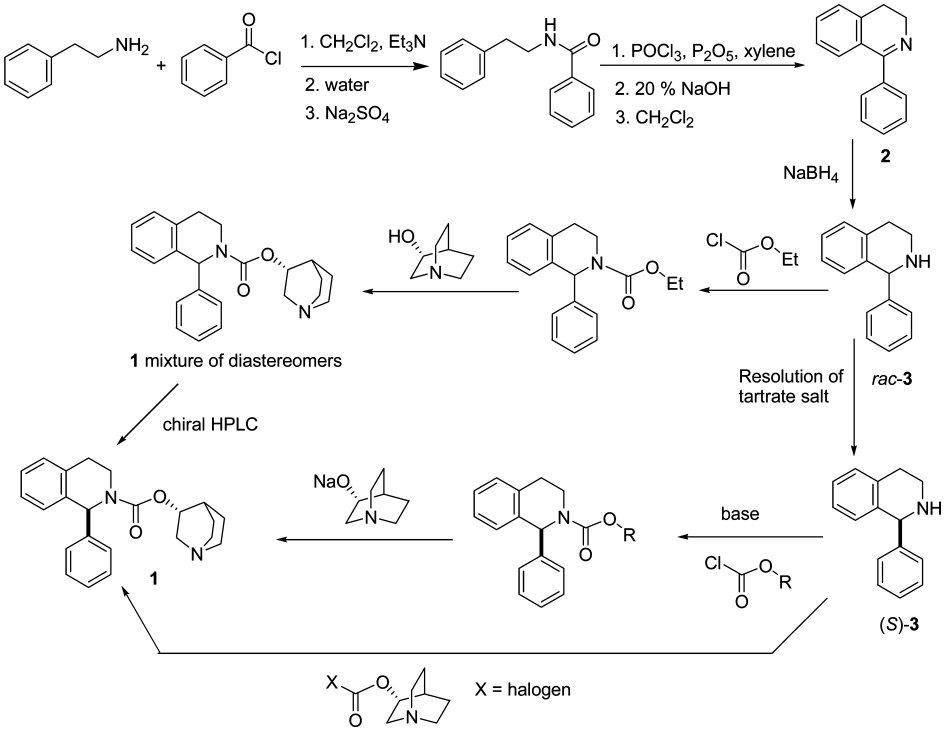
2. Catalyst Screening. Screening of selected ruthenium, rhodium, and iridium chiral catalysts was performed on the substrate **2·HCl** on small scale under transfer hydrogenation and hydrogenation conditions. We tested ruthenium-sulfonyl-diamine catalysts under both transfer hydrogenation[12,7] and hydrogenation conditions,[13] 'Noyori-type' catalyst [BINAP−$RuCl_2$−DAIPEN],[14] ruthenium and rhodium hydrogenation catalysts bearing chiral phosphines,[6] as well as iridium catalysts bearing P^N ligands.[15,8c] All of these classes of catalysts showed only moderate to low conversions and low enantioselectivity (full results of the catalyst screen are reported in the Supporting Information).

2.1. Iridium Catalysts with Diphosphine Ligands. BINAP is the most widely applicable chiral phosphine ligand.[16] We chose to run a set of initial experiments (30 bar H_2, 50 °C, 18 h, molar substrate to catalyst ratios, S/C, of 85/1) forming the catalyst in situ from $[Ir(COD)Cl]_2$ and (*R*)-BINAP in the presence of the substrate **2·HCl**.[17] High conversion (>90%) was observed in MeOH, *i*-PrOH, 1,2-dichloroethane (DCE), tetrahydrofuran (THF), and toluene, although in toluene, substrate **2·HCl** was found to have limited solubility. MeOH

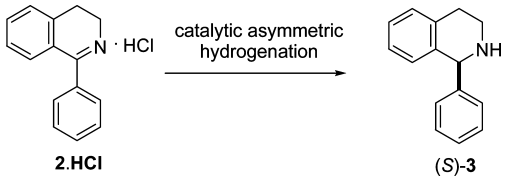
Received: March 5, 2012

   dx.doi.org/10.1021/op3000543 | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Synthetic routes to 1



Scheme 2. Asymmetric hydrogenation of 2·HCl



gave racemic **3**, while *i*-PrOH and the aprotic solvents produced, under these very preliminary reaction conditions, enantioselectivity varying between 53% and 66% ee. Following these encouraging results, a wider screen of catalysts prepared in situ from $[Ir(COD)Cl]_2$ and chiral phosphine ligands was undertaken in DCE (Figure 1, see also Supporting Information).[18]

Catalysts incorporating ligands of the BINAP and P-Phos[20] families (Figure 2) were the best catalysts in DCE. Under the conditions used, the P-Phos catalyst gave higher enantioselectivity (Figure 2, entry 4, 84% ee) than the BINAP catalyst (entry 1, 60% ee). Tol-BINAP and Tol-P-Phos produced in DCE enantioselectivity comparable to that of the 'parent' ligands BINAP and P-Phos (entries 2 and 5, 67% ee and 78% ee, respectively) while Xyl-BINAP and Xyl-P-Phos showed significantly lower enantioselectivity (entries 3 and 6, 50% ee and 49% ee, respectively).[21]

Phospholanes and P-cyclic phosphines (Ph-BPE, DuPhos, DuanPhos, CatASium D(R), Binaphane) showed low conversion and selectivity, with the exception of Binaphane (entry 12, 95% ee but only 24% conversion).[10] Paracyclophane-based (PhanePhos family) and ferrocenyl-based phosphines (BoPhoz family, JafaPhos, JosiPhos) showed low enantioselectivity with the exception of $[Ir(COD)Cl]_2$-Xyl-PhanePhos (entry 14, 78% ee), which gave only 19% conversion. Several catalysts were also tested in MeOH, but most of them gave racemic or very low ee products. Notably, iridium catalysts bearing the BDPP

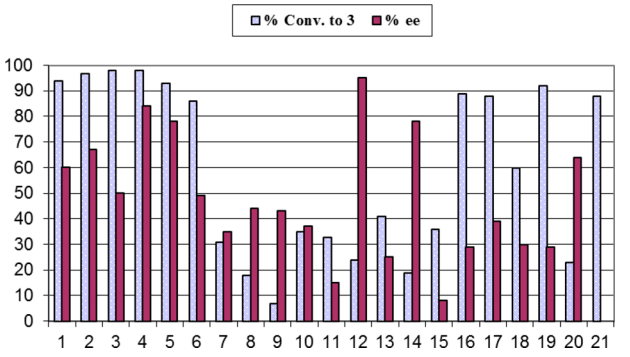
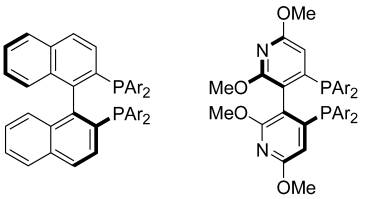


Figure 1. Screening of $[Ir(COD)Cl]_2$-phosphine catalysts in DCE (S/C 43/1, 50 °C, 30 bar H_2, 3 h); 1: (*S*)-BINAP; 2: (*R*)-Tol- BINAP; 3: (*R*)-Xyl-BINAP; 4: (*R*)-P-Phos; 5: (*S*)-Tol-P-Phos; 6: (*R*)-Xyl-P-Phos; 7: (*R,R*)-Ph-BPE; 8: (*S,S*)-Me-DuPhos; 9: (*R,R*)-*i*-Pr-DuPhos; 10: (*R,R,S,S*)-DuanPhos; 11: CatAsium D(*R*); 12: (*R*)-Binaphane; 13: (*R*)-PhanePhos; 14: (*S*)-Xyl-PhanePhos; 15: (*S*)-Me-BoPhoz; 16: (*R*)-PhEt-(*S*)-BoPhoz; 17: (*R*)-JafaPhos; 18: (*R*)-(*S*)-JosiPhos; 19: (*S,S*)-BDPP; 20: (R_a,S_c)-Naphth-Quinaphos; 21: CatASium T2.[19].



(*S*)-BINAP, Ar = Ph
(*S*)-Tol-BINAP, Ar = 4-Me-C_6H_4
(*S*)-Xyl-BINAP, Ar = 3,5-Me_2-C_6H_3

(*S*)-P-Phos, Ar = Ph
(*S*)-Tol-P-Phos, Ar = 4-Me-C_6H_4
(*S*)-Xyl-P-Phos, Ar = 3,5-Me_2-C_6H_3

Figure 2. BINAP and P-Phos family of ligands.

and phospholane ligands (DuPhos, Ph-BPE) were the only ones that gave similar results in DCE and in MeOH with

dx.doi.org/10.1021/op3000543 | Org. Process Res. Dev. XXXX, XXX, XXX–XXX

enantioselectivity in the 35−51% ee range (see Supporting Information).

2.2. Screening of Additives. It has been reported in the literature that iridium-catalyzed asymmetric hydrogenation of imines is very sensitive to the presence of additives,[6] and therefore, the hydrogenation of imine **2·HCl** was studied with the $[Ir(COD)Cl]_2$-BINAP catalyst in the presence of a variety of additives (Figure 3, see Supporting Information). THF was used as the solvent to try and maximize solubility of the different additives.

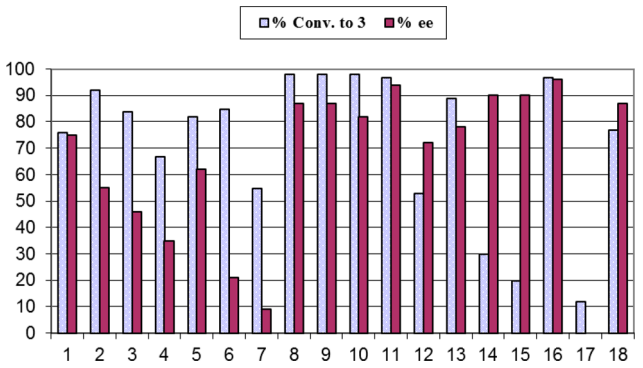


Figure 3. Screening of additives for reactions catalyzed by $[Ir(COD)Cl]_2$-BINAP catalysts, in THF (S/C 43/1, 50 °C, 30 bar H_2, 3 h). Amount of additive expressed in equivalents to substrate. 1: No additive; 2: NaI 0.2 equiv; 3: MgI_2 0.2 equiv; 4: BuN_4I 0.2 equiv; 5: BuN_4Br 0.2 equiv; 6: DABCO 0.2 equiv; 7: Piperazine 0.2 equiv; 8: H_3PO_4 (anhydrous) 1.2 equiv; 9: H_3PO_4 (aq) 1.2 equiv (85% w/w in water); 10: H_3PO_4 (anhydrous) 2.4 equiv; 11: H_3PO_4 (anhydrous) 2.4 equiv + KI 0.1 equiv; 12: AcOH 1.2 equiv (AcOH in THF); 13: AcOH 12 equiv (AcOH in THF); 14: *p*-TSOH 1.2 equiv; 15: HBF_4 (aq) 1.2 equiv (48% w/w in water); 16: (*R*)-1,1′-binaphthyl-2,2′-diyl hydrogenophosphate 1.2 equiv; 17: HCl 1.2 equiv (HCl 5 N in *i*-PrOH); 18: HCOOH 1.2 equiv (HCOOH 96% in water).

The benchmark reaction with $[Ir(COD)Cl]_2$-BINAP in THF without any additive showed 76% conversion to amine **3** over 3 h with 75% ee (*S* isomer) (Figure 3, entry 1). Iodide and bromide salts (entries 2−5), as well as amines (entries 6, 7) reduced the enantioselectivity of the reaction. Most strikingly, the addition of H_3PO_4[22] increased both activity to >97% conversion and enantioselectivity: 87% ee with 1.2 equiv of either anhydrous H_3PO_4 (entry 8) or aqueous H_3PO_4 (85% w/w in water diluted to a 0.1 M solution in THF, entry 9), 82% ee with 2.4 equiv of anhydrous H_3PO_4 (entry 10). A positive combined effect of H_3PO_4 and KI was also detected (entry 11, 94% ee), and even higher enantioselectivity was seen in the presence of a chiral acid (entry 16, 96% ee). AcOH gave reduced enantioselectivity (entries 12 and 13, 72−78% ee). The use of other acids was discarded due to reduced activity despite the good enantioselectivity: *p*-TsOH (entry 14, 30% conv., 90% ee), HBF_4 (entry 15, 20% conv., 90% ee), HCOOH (entry 18, 77% conv., 87% ee). HCl (entry 17) gave very low conversion. In addition to the experiments in THF described in Figure 3, we tested the use of KI (10%) and iodine (20%) in toluene (S/C 85/1, 50 °C, 30 bar, 16 h). In this solvent, both the use of KI (95% conversion and 42% ee) and iodine (57% conversion and 29% ee) did not improve on the benchmark reaction (95% conversion and 51% ee) (see Supporting Information).

3. Small-Scale Optimization. Having identified $[Ir(COD)Cl]_2$-BINAP and P-Phos catalysts as promising leads, a more systematic evaluation of the effect of four different solvents and two acidic additives was carried out at 50 °C, 30 bar, 16 h (Table 1). Among other positive leads identified from the experiments of Figure 3, we did not pursue the use of chiral acids due the potential cost contribution.

CH_2Cl_2. CH_2Cl_2 was used as representative chlorinated solvent in replacement for DCE, used in previous experiments. The reactions in CH_2Cl_2 (clear solutions) gave full conversion at S/C 170/1 overnight (50 °C, 30 bar) with both $[Ir(COD)Cl]_2$-BINAP (81% ee) and $[Ir(COD)Cl]_2$-P-Phos (85% ee) catalysts in the absence of any additive (entry 1). The addition of phosphoric acid (entry 2) gave a cloudy solution and suppressed the reaction, while the addition of AcOH (entry 3) was either neutral (BINAP: 81% ee) or slightly favorable (P-Phos: 87% ee). In the absence of any additive, the enantioselectivity decreased when the catalyst loadings were reduced (entry 4). Upon addition of AcOH the enantioselectivity at S/C 425/1 (entry 5) was higher than in the absence of an additive (entry 6), although not as high as at S/C 170/1 (entry 3).

Toluene. Modest enantioselectivity was obtained in neat toluene with $[Ir(COD)Cl]_2$-BINAP (60% ee, entry 6, similar to the 57% ee obtained in preliminary experiments). The behavior seen for the reactions in CH_2Cl_2 was mirrored by the results of reactions in toluene: conversion decreased with phosphoric acid (entry 7), and a good increase in enantioselectivity was seen when AcOH was added (entry 8, up to 82% ee with BINAP).

i-PrOH. $[Ir(COD)Cl]_2$-BINAP gave moderate enantioselectivity at S/C 170/1 in neat *i*-PrOH (72% ee, entry 10) and in the presence of AcOH (entry 12, 70% ee). *i*-PrOH/H_3PO_4 was the only solvent/acid system tested where the BINAP-based catalyst (entry 11, 90% ee at 30 bar, S/C 170/1) matched or surpassed the enantioselectivity obtainable with the P-Phos-based catalyst (entry 11, 86% ee at 30 bar, S/C 170, and entry 13 and 91% ee at 5 bar, S/C 425/1).

Me-THF. Both $[Ir(COD)Cl]_2$-BINAP and $[Ir(COD)Cl]_2$-P-Phos gave low enantioselectivity at S/C 170/1 (36−39% ee) in neat Me-THF (entry 14) and in the presence of AcOH (entry 16). Enantioselectivity with $[Ir(COD)Cl]_2$-BINAP in Me-THF/H_3PO_4 was significantly higher (78% ee, entry 15), but not as high as the one detected in THF/H_3PO_4 (entries 17−20).

THF. The enantioselectivity obtained in neat THF with $[Ir(COD)Cl]_2$-BINAP (66% ee, entry 17) was significantly increased by addition of H_3PO_4 (entry 18, 87% ee). In this specific solvent, THF, the use of AcOH had already been proven to be inferior to the use of H_3PO_4 (see Figure 3, entries 12 and 13). The use of $[Ir(COD)Cl]_2$-P-Phos in THF/H_3PO_4 (entries 18−24) provided the highest enantioselectivity values so far encountered (entries 23 and 24, up to 95% ee). The enantioselectivity of the reaction was not generally improved by the use of lower reaction temperature (40 °C, entry 19) nor by the use of lower hydrogen pressures (entries 18, 19, and 24, 5 bar). Contrary to the preliminary result reported in Figure 3, the addition of 0.1 equiv of KI in the presence of H_3PO_4 produced no advantage once retested at S/C 170/1 (entry 21) and was not further investigated. A small increase in the reaction temperature from 50 °C (entry 23) to 60 °C (entry 24) gave full conversion at S/C 425/1 without affecting the enantioselectivity. From the point of view of practicality, it was determined that the use of aqueous phosphoric acid (85% H_3PO_4 in water, diluted in THF prior to addition to the reaction mixture, entries 18 and 22) was equally effective as the

dx.doi.org/10.1021/op3000543 | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 1. Hydrogenation of 2·HCl with $[Ir(COD)Cl]_2$-BINAP and P-Phos catalysts with different acids and solvents[a]

			(S)-BINAP		(S)-P-Phos	
entry	S/C	additive (equ iv)	3 (%)[b]	3 ee (%)[b]	3 (%)[b]	3 ee (%)[b]
			CH_2Cl_2			
1	170/1	–	>97	81	>97	85
2	170/1	H_3PO_4 (s) (2.4)	10	nd	6	nd
3	170/1	AcOH (2)	>97	81	>97	87
4	425/1	–	>97	67	>97	72
5	425/1	AcOH (2)	>97	74	>97	80
			Toluene			
6	170/1	–	>97	60		
7	170/1	H_3PO_4 (s) (2.4)	55	nd		
8	170/1	AcOH (2)	>97	82	94	88
9	425/1	AcOH (2)	>97	77	>97	86
			i-PrOH			
10	170/1	–	96	72		
11	170/1	H_3PO_4 (s) (2.4)	>97	90	>97	86
12	170/1	AcOH (2)	>97	70		
13[c]	425/1	H_3PO_4 (s) (2.4)			94	91
			MeTHF			
14	170/1	–	88	36		
15	170/1	H_3PO_4 (s) (2.4)	82	78		
16	170/1	2 (AcOH)	74	38	88	39
			THF			
17	85/1	–	>97	66		
18[d]	43/1	H_3PO_4 (aq) (1.2)	>97	87 (88)[e]		
19[f]	43/1	H_3PO_4 (s) (2.4)	25(30)[e]	86 (87)[e]	17 (18)[e]	88[e]
20[g]	170/1	H_3PO_4 (s) (2.4)	98	87	>97	94
21	170/1	H_3PO_4 (s) (2.4) + KI (0.1)	>97	82	>97	92
22	170/1	H_3PO_4 (aq) (1.2)			>97	93
23	340/1	H_3PO_4 (s) (2.4)			97	95
24[h]	425/1	H_3PO_4 (s) (2.4)			>97	95 (92)[e]

[a]Reactions run in Biotage Endeavour: substrate, $[Ir(COD)Cl]_2$ (1 mg, 0.0015 mmol), phosphine (0.0033 mmol) in 3−5 mL solvent + additive. Reactions were run at 50 °C, 30 bar, 16 h. [b]Conversion and enantioselectivity measured by HPLC (CHIRALPAK AD-H column). [c]Reaction run at 65 °C, 5 bar, 40 h. [d]Reactions run for 3 h. [e]In brackets conversion and ee obtained under the same conditions at 5 bar hydrogen. [f]Reactions run for 3 h at 40 °C. [g]Reactions run at 5 bar. [h]Reaction run at 60 °C. nd = not determined.

use of the anhydrous phosphoric acid that was added as a solid to the reagents at the screening stage.

The results reported in Table 1 highlight the remarkable dependence of the reaction's enantioselectivity upon the combination of solvent and acidic additive. Several choices were open at this stage of the research. Not yet having developed an effective crystallization process for ee upgrade of product **3**, it was decided to pursue the option that had been demonstrated to provide the highest enantioselectivity: $[Ir(COD)Cl]_2$-P-Phos in THF/H_3PO_4. Small-scale optimization in the Biotage Endeavour was continued using $[Ir(COD)Cl]_2$-P-Phos in THF with aqueous phosphoric acid (Table 2). The reactions were driven to full conversion at progressively lower catalyst loadings by the combined effect of increased reaction temperatures, reaction pressure and longer reaction times. At S/C 850/1 the combination of 65 °C/20 or 30 bar (entries 2 and 3) was found to be more effective than the combination of 70 °C/10 bar (entry 4). A good result was finally obtained at S/C 1275/1, 60 °C, 30 bar with full conversion and 94% ee (entry 5). The use of lower pressure (10 bar) led to incomplete conversion, even after 64 h reaction time (entry 6).

4. Hydrogenations on Multigram Scale. While the conclusion that could be drawn from the experiments of Table 2 was that the reaction would benefit from the use of highest achievable pressure and high substrate concentration, the following experiments in standalone Parr autoclaves (50 mL, 100 and 600 mL autoclaves, benchtop Parr Microreactors series 5500) mainly aimed at demonstrating the reaction feasibility within the constraints of the equipment available for scale-up (a 10 L Biazzi reactor operating at 20 bar maximum hydrogen pressure). The parameters of substrate concentration and the related parameter of phosphoric acid concentration were fixed respectively at 0.37−0.41 M and 1.8 equiv, of H_3PO_4/substrate (Scheme 3, Table 3).

Table 2. Best reaction conditions with $[Ir(COD)Cl]_2$-(S)-P-Phos catalyst in THF/phosphoric acid in Biotage Endeavour.[a]

entry	S/C	equiv H_3PO_3	conc (M)	temp (°C)	press (bar)	time (h)	3 (%)[b]	3 ee (%)[b]
1	850/1	1.8	0.64	60	30	72	95	96
2	850/1	1.8	0.64	65	20	72	>198	95
3	850/1	2.4	0.64	65	30	72	>98	96
4	850/1	1.8	0.64	70	10	72	95	96
5	1275/1	1.8	0.75	60	10	64	68	95
6	1275/1	1.8	0.75	60	30	64	98	94

[a]Reactions run in Biotage Endeavour: substrate, $[Ir(COD)Cl]_2$ and 1.1−1.2 equiv of phosphine per Ir in 3−6 mL solvent + additive. [b]Conversion and enantioselectivity measured by HPLC (CHIRALPAK AD-H column).

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Scheme 3. Best reaction conditions for asymmetric hydrogenation of 2·HCl

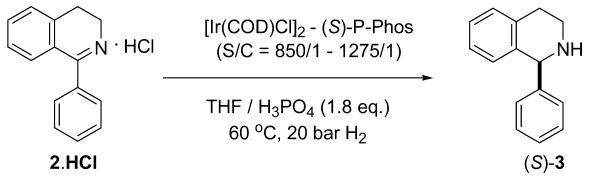

Table 3. Hydrogenation of 2·HCl with $[Ir(COD)Cl]_2$-(*S*)-P-Phos catalysts (solvent THF, additive 1.8 equiv of H_3PO_4 (aq), 60°C and 20 bar H_2)[a]

entry	S/C	scale (mmol)	conc (M)	time (h)	3 (%)[b]	3 ee (%)[b]
			50 mL Autoclave			
1	850/1	5.1	0.41	45	>99	95
2[c]	850/1	5.1	0.41	45	>99	93
3	1060/1	5.1	0.41	72	>98	93.5
4	1275/1	5.1	0.41	72	>99	95
5[c]	1275/1	5.1	0.41	72	>99	95
6[d]	1275/1	5.1	0.41	60	>99	87
7	1700/1	5.1	0.41	60	>99	95
8	2125/1	6.4	0.47	90	>99	95
			100 mL Autoclave			
9	850/1	15.3	0.41	72	>99[f]	95
10[e]	1275/1	12.8	0.41	60	98[f]	95
			600 mL Autoclave			
11	850/1	85.0	0.41	68	>99	95
12[e]	850/1	63.8	0.38	65	>99	94
13[e]	1275/1	63.8	0.38	68	92	95
				133	>99	95
			10 L Reactor[g]			
14	1060/1	830.8	0.37	47	98	97
15	1060/1	1158.2	0.37	48	97	95.5

[a]Reaction conditions: substrate, $[Ir(COD)Cl]_2$ and phosphine (1.1 to 1.2 equiv to Ir) were placed in the autoclave and purged with nitrogen; then a solution of H_3PO_4 (85% in H_2O) in THF was added. The reaction was purged with nitrogen and hydrogen, pressurized with hydrogen, and heated. [b]Conversion and enantioselectivity were measured by HPLC on a CHIRALPAK AD-H column. [c]Reactions run at 65 °C and 10 bar H_2. [d]$[Ir(COD)Cl]_2$-(*S*)-BINAP catalyst. [e]HPLC grade solvent used without predegassing. [f]96% conversion after some solid stuck on top of the autoclave was dissolved and added to the solution. [g]Conversion measured by HPLC on Ascentis Express C8 and enantioselectivity measured by HPLC on CHIRALPAK IB column.

The best reaction conditions obtained in the Biotage Endeavour were tested in 50 mL Parr autoclaves and full conversion with good enantioselectivity was achieved, although under prolonged reaction times. The use of 60 °C/20 bar (Table 3, entries 1 and 4) gave higher enantioselectivity than the combination of 65 °C/10 bar (entries 2 and 5). Full conversion with consistent ee (~95% ee) was obtained at catalyst loading as low as S/C 2125/1 (entry 8). One reaction was run in the presence of (*S*)-BINAP (entry 6) and confirmed that the $[Ir(COD)Cl]_2$-(*S*)-BINAP had very similar activity to $[Ir(COD)Cl]_2$-(*S*)-P-Phos but gave lower enantioselectivity (87% ee). The reactions with the $[Ir(COD)Cl]_2$-(*S*)-P-Phos system were repeated in a similar 100 mL autoclave on 3.10 to 3.75 g scale at S/C 850/1 (entry 9) and at S/C 1275/1 (entry 10). The reactions gave full conversion but some starting material was found unreacted on the top of the vessel, highlighting the importance of achieving efficient mixing and dissolution of the starting material. Two hydrogenations were run in 600 mL autoclaves at S/C 850/1 on 20.7 g scale (85 mmol, entry 11) and on 15.5 g scale (64 mmol, entry 12), giving full conversion and 94−95% ee. A third reaction was run on 15.5 g scale (64 mmol, entry 13) at S/C 1275/1 giving just 92% conversion after 68 h. The reduced conversion was attributed to a problem with the stirrer, which limited agitation of the reaction. After 68 h the reaction was opened to air, the problem with the stirrer was corrected; the reaction was allowed to proceed for further 65 h to give full conversion and 95% ee.

Different work up procedures were tested (see Supporting Information). Concentration of the reaction mixture by removal of THF followed by workup with dichloromethane or AcOEt and diluted aqueous base (KOH or ammonia) gave high mass recovery of amine **3**. A recrystallization procedure was developed (see Supporting Information) from *i*-PrOH/water to give pure amine **3** with enantiopurity upgrade from 97% ee to 99% ee, in 78% yield.[23] Larger batches of 200 g of imine **2·HCl** were subjected to hydrogenation (entries 14 and 15) according to the best procedure developed on small scale, which was repeated without problems. The crude product mixture showed in both cases >97% HPLC purity and, pleasingly, a slightly higher enantioselectivity than previously detected (97% ee and 95.5% ee respectively, based on a more accurate analytical method that had been developed in the meantime). An improved workup procedure using KOH/EtOAc was applied and afforded the product **3** in quantitative yield. An improved recrystallization procedure from *i*-PrOH/H_2O 1/3 (95% isolated yield) led to increased HPLC purity (99.2%), with an enantiomeric purity of 98% ee.[24]

CONCLUSIONS

We have demonstrated the feasibility of an efficient process for the asymmetric hydrogenation of the hydrochloride salt of 1-phenyl-3,4-dihydro-isoquinoline (**2·HCl**). Unlike many other members of the class of 1-substituted-3,4-dihydroisoquinolines, phenyl-substituted imine **2** is a challenging substrate for asymmetric reductions. We found that the use of the hydrochloride salt as the substrate gave increased reactivity in the presence of iridium catalysts prepared in situ from readily available biaryl-phosphine chiral ligands (BINAP and P-Phos). Through a broad screen of catalysts followed by extensive small-scale optimization with different combinations of solvents and acids we have identified specific reaction conditions providing high enantioselectivity at acceptably low catalyst loadings (S/C > 1000/1). The robustness of the reaction has been proven by reproducing it on 200 g scale to give (*S*)-**3** with 95% isolated yield, 98% ee, and >99% HPLC purity.

EXPERIMENTAL SECTION

Synthesis of *N*-Phenethylbenzamide. Phenethylamine (3.86 mmol, 468 g, 486 mL) and CH_2Cl_2 (2.25 L) were charged into a 10 L reaction vessel and cooled to 0 − 5 °C. Benzoyl chloride (3.88 mmol, 545 g, 450 mL) was added slowly over 2 h. NEt_3 (4.46 mmol, 451 h, 621 mL) was added to the white reaction suspension over 1 h at 0−5 °C. The reaction mixture was heated to reflux for 5 h and then cooled to room temperature overnight, under stirring. Purified water (3 L) was added, and the phases were separated. The organic phase was washed with water (1.5 L) and dried over Na_2SO_4 (50 g). The

dx.doi.org/10.1021/op3000543 | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

solvent was evaporated to give *N*-phenethylbenzamide (525 g, 60% yield) as a white to yellow crystalline powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.82 (t, J = 7 Hz, 2H, CH_2-Ph), 3.45 (t, J = 7 Hz, CH_2-N), 7.16−7.28 (m, 5H), 7.28−7.45 (m, 3H), 7.78 (d, J = 7 Hz, 2H), 8.5 (sb, 1H, N*H*). ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 35.5, 41.3, 126.5, 127.5, 128.7, 128.8, 129.1, 131.5, 135.0, 140.0, 166.6.

Synthesis of 1-Phenyl-3,4-dihydroisoquinoline (2). *N*-phenethylbenzamide obtained in the previous step (1.15 mmol, 260 g) and 2 L of xylene were added into a 10 L reaction vessel. To this mixture $POCl_3$ (3.62 mmol, 556 g, 338 mL), P_2O_5 (2.34 mmol, 332 g), and additional 1.12 L of xylene were added. The reaction mixture was heated to 140 °C (temperature of the reactor jacket). The reaction was cooled after 5 h to room temperature, and 1.5 kg of ice was slowly added to the reaction mixture (the order of addition was determined by the fact that the product was obtained as a melted residue on the bottom of the reactor, which precluded isolation by adding it to ice). An exothermic reaction occurred. Additional 2 L of purified water was added, and the reaction mixture was stirred overnight at room temperature. The two phases were separated, the water layer was transferred into a 10 L reactor, and the pH was adjusted to 10−11 using a 20% solution of NaOH (6 L). It was washed with 2 × 1.95 L of CH_2Cl_2. The organic phases were combined, the solvent was evaporated, and 211 g of an oily product (88% yield if **2**) was obtained. The crude product was used directly in the next step.

Synthesis of 1-Phenyl-3,4-dihydroisoquinoline·HCl (2·HCl). 1-Phenyl-3,4-dihydroisoquinoline **1** (190 g) from the previous step was dissolved in TBME (190 mL). A solution of 126 g HCl g in 2.5 L of TMBE was added to give a suspension that was stirred for one hour. The product was collected by filtration to give 208 g of **2·HCl** (93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.22 (t, J = 8 Hz, 2H, CH_2-Ph), 3.98 (t, J = 8 Hz, CH_2-N), 7.40 (m, 1H), 7.50 (m, 1H), 7.63 (m, 1H), 7.68 (m, 2H), 7.84 (m, 4H), 14 (sb, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) 24.6, 41.0, 125.6, 127.8, 128.7, 128.8, 129.6, 130.8, 132.9, 133.6, 136.5, 139.5, 172.6. Cl analysis; calculated for $C_{15}H_{14}NCl$: 14.55, found: 14.44. Mp: 218−222 °C.[25]

Hydrogenation of 2·HCl on 15.5 g Scale in 600 mL Autoclave (S/C 850/1, entry 12, Table 3). *Hydrogenation.* $[Ir(COD)Cl]_2$ (0.0375 mmol, 25 mg), (*S*)-P-Phos (0.086 mmol, 1.15 equiv to Ir, 55.5 mg) and imine **2·HCl** (63.7 mmol, 15.52 g) were placed in a stainless steel 600 mL Parr autoclave. The autoclave was sealed and placed under nitrogen. THF (165 mL) and H_3PO_4 (85% in water, 7.9 mL, 115 mmol) were premixed and then added to the solid in the autoclave using a 50 mL syringe through the autoclave injection port. The autoclave was sealed and then purged with nitrogen five times by pressurizing to 3 bar under stirring and then releasing pressure. The reaction was then purged with hydrogen five times. The pressure was set to 20 bar, and the reaction was heated to 60 °C over ∼30 min (pressure increased to about 22 bar). The reaction was stirred at maximum stirring speed (1200−1500 rpm) for 65 h, then it was cooled to 45 °C and opened to find a clear, thick yellow/green solution that was sampled. HPLC analysis showed full conversion to amine **3** and 94% ee (*S*)-enantiomer.

Workup. The reaction was diluted with MeOH (∼200 mL), transferred to a round-bottomed flask, and concentrated under reduced pressure to obtain a clear-yellow/-green oil. CH_2Cl_2 (100 mL) was added, followed by 50 mL of water and 60 mL of 25% ammonium hydroxide (to constant pH 8/9). The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (4 × 100 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filter cake was washed with more CH_2Cl_2 (2 × 75 mL). The CH_2Cl_2 solution was evaporated under reduced pressure to give an off-white solid (>99% amine **3**, 94.5% ee, 13.8 g). At this stage, the isolated yield was not established.[23]

Recrystallization. Amine **3** (13.1 g) from the previous step was placed in a 250 mL round-bottomed flask equipped with an air condenser. Water (50 mL) and *i*-PrOH (50 mL) were added, and the reaction was heated to 90 °C (oil bath, external temperature) to obtain a clear-yellow solution. The reaction was allowed to cool to room temperature to give a thick, white suspension that was diluted with 50 mL water and collected by filtration. The off-white solid was allowed to dry on the filter for two days and then was further dried under reduced pressure (13.1 g, 88% yield). HPLC analysis showed >99% purity of 1-(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline, **3**, with 94.5% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.19 (s, 1H, N*H*), 2.75 (m, 1H), 3.00 (m, 2H), 3.20 (m, 1H), 5.02 (s, 1H), 6.67 (d, J = 9 Hz, 1H), 6.95 (m, 1H), 7.08 (d, J = 4 Hz, 2H), 7.16−7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 31.4, 43.9, 63.7, 127.3, 128.0, 129.1, 129.8, 130.1, 130.69, 130.72, 137.1, 139.9, 146.5.

HPLC Method. Both conversion and enantioselectivity were determined using a CHIRALPAK AD-H, 0.46 cm× 25 cm; eluent: isocratic, hexane/EtOH, 98.5:1.5 + 0.1% Et_2NH; flow: 1 mL/min; temperature: 30 °C; detection: 220 nm. Imine **2** eluted at 7.5 min; (*S*)-**3** enantiomer at 9 min and (*R*)-**3** enantiomer at 12 min.

Hydrogenation of 2·HCl on 202 g Scale in 10 L Biazzi Reactor (S/C 1060/1, entry 14, Table 3). *Hydrogenation.* Imine **2·HCl** (202.5 g, 0.8308 mol), 103 mL of 85% H_3PO_4, $[Ir(COD)Cl]_2$ (0.39 mmol, 0.263 g), (*S*)-P-Phos (0.9 mmol, 0.579 g), and 2.15 L of THF, were added to the reactor. The reaction mixture was purged with nitrogen and hydrogen, pressurized with hydrogen (20 bar), heated to 60 °C, and stirred. After 47 h HPLC analysis of the crude reaction mixture showed 97% HPLC purity of **3** and 97% ee. The walls of the reactor were washed with 100 mL of THF, and 1.11 L of MeOH was added to the reaction mixture. The solvent was evaporated, and an oily residue (418 g) was obtained. HPLC analysis showed 97.8% HPLC purity, 97% ee and 41.8% HPLC assay of **3** (quantitative yield).

Workup. Crude product (390 g) of the from the previous step was charged into the reactor; 3.75 L of AcOEt and 3.75 L of KOH 4 M aqueous solution were added, and the mixture was stirred for one hour at room temperature. The phases were separated, the water phase was extracted with 3.75 L of AcOEt, the organic phases were combined, and the solvent was evaporated. A quantity of 170 g of light-yellow crystalline product was obtained. HPLC analysis showed 98% HPLC purity and 95.6% HPLC assay of **3** (quantitative yield).

Recrystallization. Crystalline product **3** (169 g) of from the previous step was charged in a 10 L reactor; 1.69 L of *i*-PrOH was added, and the mixture was heated to 83 °C until the solution was clear. The mixture was cooled to 0−5 °C over 2 h, 5.07 L of water was added, and the mixture was stirred for 30 min. The product was filtered off, washed with 0.27 L of water, and dried until loss on drying (LOD) was stable. HPLC analysis showed 99.2% purity and 97.8% ee (153 g of crystallized 1-(*S*)-phenyl-1,2,3,4-tetrahydroisoquinoline, (*S*)-**3**,

dx.doi.org/10.1021/op3000543 | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

95% isolated yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.46 (s, 1H, N*H*), 2.69 (m, 1H), 2.88 (m, 2H), 3.06 (m, 1H), 4.97 (s, 1H), 6.59 (d, J = 4 Hz, 1H), 6.96 (m, 1H), 7.06 (m, 2H), 7.2−7.3 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): 29.55, 42.0, 61.5, 125.7, 126.3, 127.4, 128.0, 128.5, 129.3, 129.4, 135.8, 139.1, 145.5. CHN analysis; calculated for $C_{15}H_{15}N$: C 86.08, H 7.22, N 6.69; found: C 85.83, H 7.26, N 6.68. Mp: 86.5 °C,[3,26] $[\alpha]_D$ = +4.0° (c = 1, MeOH, T = 20 °C).

HPLC Analytical Methods. The reactions were analyzed for conversion using an Ascentis Express C8 column, 2.7 μm particles, 100 mm × 4.6 mm i.d., Detection: 210 nm; Flow: 0.7 mL/min, 25 °C; Eluent A: 0.02 M Na_2HPO_4 adjusted to pH 2.5 by addition of H_3PO_4; Eluent B: acetonitrile. 85:15 A/B for 3 min, then gradient to 40:60 A/B for 10 min. The reactions were analyzed for enantioselectivity using a CHIRALPAK IB column, 250 mm × 4.6 mm, 5 μm, 0.46 cm × 25 cm; eluent: isocratic hexane/EtOH/MeOH, 90:4:6 + 0.2% TFA; flow: 1 mL/min; temperature: 25 °C; detection: 220 nm. (*S*)-**3** enantiomer at 7.9 min and (*R*)-**3** enantiomer at 10.7 min.

■ ASSOCIATED CONTENT

Supporting Information

Full results of the catalyst screen and small-scale optimization reaction, HPLC analytical methods, representative NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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