Organic Process Research & Development

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pubs.acs.org/OPRD

Catalytic Asymmetric Reduction of a 3,4-Dihydroisoquinoline for the Large-Scale Production of Almorexant: Hydrogenation or Transfer Hydrogenation?

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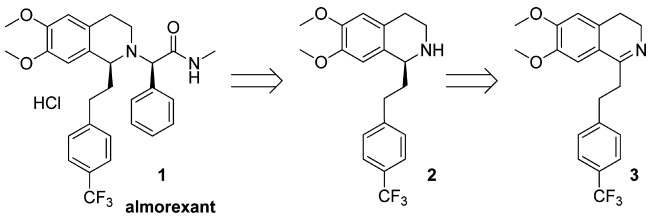
Supporting Information

ABSTRACT: Several methods are presented for the enantioselective synthesis of the tetrahydroisoquinoline core of almorexant (ACT-078573A), a dual orexin receptor antagonist. Initial clinical supplies were secured by the Noyori Ru-catalyzed asymmetric transfer hydrogenation (Ru-Noyori ATH) of the dihydroisoquinoline precursor. Both the yield and enantioselectivity eroded upon scale-up. A broad screening exercise identified TaniaPhos as ligand for the iridium-catalyzed asymmetric hydrogenation with a dedicated catalyst pretreatment protocol, culminating in the manufacture of more than 6 t of the acetate salt of the tetrahydroisoquinoline. The major cost contributor was TaniaPhos. By switching the dihydroisoquinoline substrate of the Ru-Noyori ATH to its methanesulfonate salt, the ATH was later successfully reduced to practice, delivering several hundreds of kilograms of the tetrahydroisoquinoline, thereby reducing the catalyst cost contribution significantly. The two methods are compared with regard to green and efficiency metrics.

INTRODUCTION

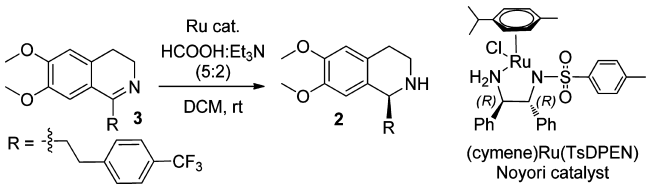
In 2005, Actelion Pharmaceuticals disclosed a 1,2,3,4-tetrahydroisoquinoline derivative (almorexant, **1**) (Scheme 1) as an efficient antagonist for orexin receptors. Orexins are hypothalamic peptides that play an important role in the sleep–wake cycle of mammals. At the time, almorexant was the first compound active on both the orexin OX(1) and OX(2) receptors. Because of its novel mechanism of action, it appeared as a very promising drug for the treatment of sleeping disorders.[1] The preparation of almorexant requires the synthesis of an enantiopure key intermediate, **2**, that could be obtained by asymmetric reduction of the corresponding 3,4-dihydroisoquinoline **3**.

Scheme 1. Almorexant and Its Key Intermediates



Historical Background of the Preparation of Enantiopure 2. A large number of methods for the enantioselective reduction of this class of cyclic imines have been reported in the literature.[2] Since the seminal paper of Noyori and co-workers,[3] transfer hydrogenation with a chiral N-sulfonated diamine–Ru(II)–η^6-arene catalyst has been the method of choice.[4] In most cases, the reducing agent is a 5:2 HCOOH/Et_3N mixture (TEAF), leading to the formation of the desired product with high enantiomeric excess (ee). The initial trials with the Noyori catalyst performed at Actelion Pharmaceuticals Ltd. were promising. Using a standard Ru(cymene)(Ts-DPEN) catalyst, the desired product (Scheme 2) was obtained in high yield (95%) with good ee's (81–95%) at substrate to catalyst (S:C) ratio of 500 on a 250–300 g scale. The formation of the HCl salt of the product in methanol allowed enantiomeric enrichment up to 99% ee. Unfortunately, these good results were not reproducible on a larger scale. During a 30 kg campaign performed at a toll manufacturer, a severe drop in the yield (57–60%) and ee (76–80%) was observed in addition to

Scheme 2. Asymmetric Transfer Hydrogenation of 3



Received: September 26, 2013
Published: November 22, 2013

   dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531–1539

the presence of a byproduct, the *N*-formylated tetrahydroisoquinoline. Such a process with varying results was judged unfit for longer-term production. Alternative routes relying on nonenantioselective hydrogenation and classical resolution were designed. Upon screening of a set of chiral acids, D-tetranilic acid[5] was identified as a good resolving agent, leading to 41% yield of the desired diastereoisomer with 98% ee. The undesired enantiomer could be recycled via oxidation to the imine with low-cost bleach.[6] Although this protocol delivered the desired intermediate with a high level of purity, an asymmetric synthesis route was more desirable in order to increase the overall yield and limit the numerous solvent switches due in part to the recycling steps.

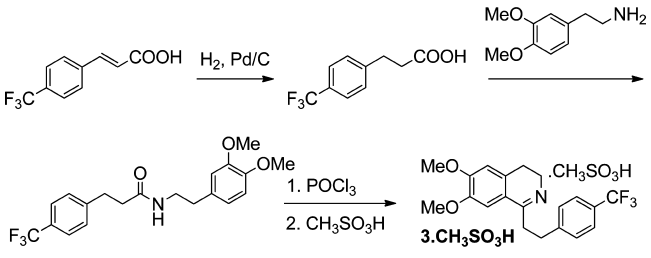
Hence, a route relying on catalytic asymmetric hydrogenation (AH) of the cyclic imine was investigated. Hydrogenation of 3,4-dihydroisoquinoline with molecular hydrogen has also been reported with different metals such as Ti, Ru, Rh, and Ir.[7] Catalyst screening was performed by a commercial screening company using 11 ligands from four classes of bidentate phosphines along with various metal precursors and solvents. Modest results were obtained with Ir (maximum 56% ee).

There have been several reports by DSM on catalytic asymmetric hydrogenation processes using the proprietary MonoPhos library (codeveloped with the University of Groningen)[8] or other readily available catalytic systems and/or ligands.[9] In this paper, we present the initial search for a cost-efficient asymmetric hydrogenation catalyst, resulting in the selection of a very effective iridium–TaniaPhos-based catalyst for the enantioselective conversion to **2** that was used on a ton scale. However, the high cost contribution of this latter catalyst triggered the search for a more competitive alternative. We chose to revisit the route based on asymmetric transfer hydrogenation (ATH) that was originally developed by Actelion Pharmaceuticals Ltd. A second process for the multikilogram production of intermediate **2** based on a Noyori Ru catalyst was then developed. The pros and cons of the two catalytic technologies—asymmetric hydrogenation and asymmetric transfer hydrogenation—for this particular compound will be presented as well as a justification for our final catalyst choice.

RESULTS AND DISCUSSION

The cyclic imine **3** was prepared in three steps from commercially available *trans*-4-(trifluoromethyl)cinnamic acid (Scheme 3).[1] The ring formation was accomplished via the Bischler–Napieralski reaction of the corresponding amide, with the product being isolated as its mesylate salt, **3·CH$_3$SO$_3$H**. Depending on the reduction method used, the substrate was either used as such or first converted to the free base.

Scheme 3. Synthetic Route towards Imine 3



1. Solvent Screening with a Phosphoramidite Ligand-Based Hydrogenation Catalyst. The DSM screening procedure for an asymmetric hydrogenation catalyst first involves the identification of the best reaction conditions for a given class of catalysts. A representative member of the catalyst class is then chosen and tested in different solvents at different H_2 pressures and temperatures in the presence or absence of additives. The experiments are carried out in a medium-throughput parallel Endeavor reactor where up to eight hydrogenations can be run in parallel.[10] On the basis of earlier results, we anticipated that Ir would be more efficient than Rh for the catalytic asymmetric hydrogenation of imine **3**, using as the ligand a phosphoramidite with substituents at the 3- and 3′-positions (**L2** in Figure 1) instead of the standard ligand MonoPhos (**L1**).[11] In Figure 1, we show the results of the solvent screening.

As is often the case in asymmetric hydrogenations, the solvent played an important role. Nonprotic solvents such as dichloromethane (DCM), ethyl acetate (EtOAc), methyl *tert*-butyl ether (MTBE), and methyl ethyl ketone (MEK) gave the best results in terms of ee together with acceptable conversions. The highest conversions were obtained with acetic acid as the solvent or as an additive in DCM, albeit with low ee's. Acids can indeed scavenge the amine product as its salt and prevent catalyst inhibition.[12] (*S*)-MonoPhos was also tested under the same conditions in DCM and gave 67% conversion with only 17% ee, confirming the superiority of bulkier phosphoramidites for the desired transformation.

2. Reaction Condition Screening Using Four Ligands and Robotic Equipment. With the aid of robotic equipment and a high-throughput A96 parallel reactor,[13] we explored the influence of Ir precursors and additives in 96 reactions in parallel. Since the discovery of the Metolachlor imine hydrogenation catalyst,[14] iodine is commonly used to improve the performance of Ir catalysts in imine hydrogenation.[15] Phthalimide has also been reported as an efficient additive.[16] Two Ir precursors, $Ir(COD)_2BF_4$ and $[Ir(COD)Cl]_2$ (cationic and neutral, respectively) were used together with two bulky phosphoramidite ligands (*R*)-**L2** and (*S*,*S*,*S*)-**L3** (the latter being sterically hindered on the amine side), the axially chiral ligand **L4**, and a ferrocene-based ligand from the Solvias collection, **L5**. The resulting catalysts were tested in four solvents (EtOAc, MIBK, DCM, and IPA) in the absence or presence of I_2 or phthalimide as an additive, thus generating a total of 96 different catalytic mixtures, all tested in parallel within 24 h (Scheme 4).

The color-coded table in Scheme 4 shows that most of the ee's obtained are lower than 50%. Regardless of the ligand, the precursor $[Ir(COD)Cl]_2$ (**Ir 2**) appeared to be much better than $Ir(COD)_2BF_4$ (**Ir 1**). In the case of the two phosphoramidite ligands, the best results were obtained in EtOAc (62–66% ee), while the use of IPA resulted in very low ee's. Overall, iodine had a negative effect on the performance of the phosphoramidite/Ir catalysts, while the presence of phthalimide did not have much influence. From the non-phosphoramidite reactions only one specific combination stands out: the ferrocene-based ligand **L5** in the presence of I_2 with EtOAc as the solvent and $[Ir(COD)Cl]_2$ as the metal source gave 76% ee.

3. Further Investigation of the MonoPhos Lead. Having set the reaction conditions for the Ir/phosphoramidite catalyst ($[Ir(COD)Cl]_2$ as the Ir source, no additive, EtOAc as the solvent), we varied the phosphoramidite ligands in order to

dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531–1539

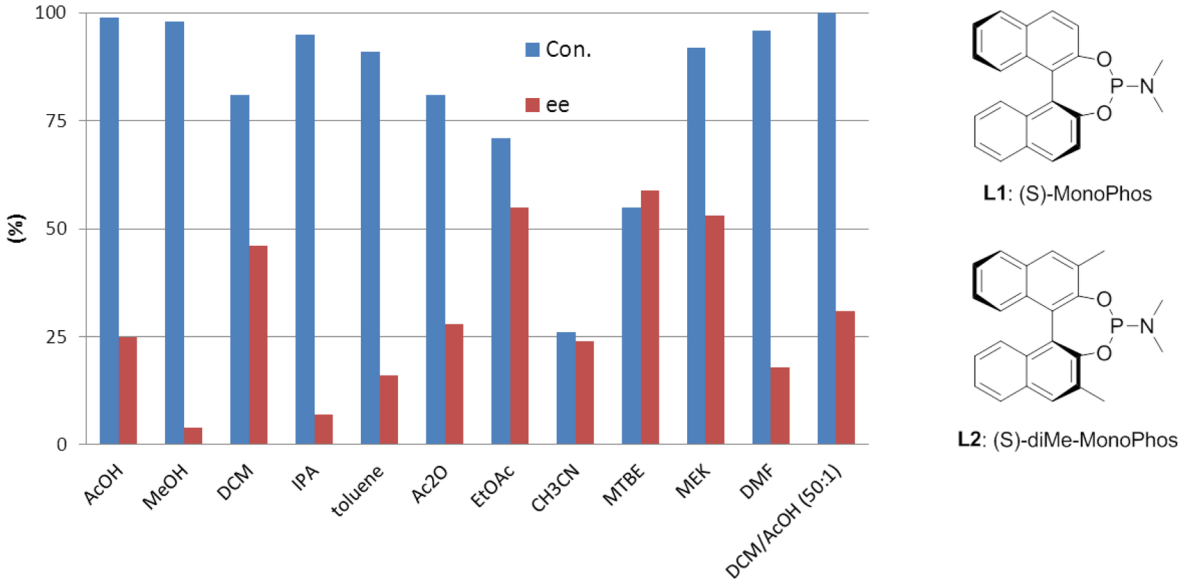


Figure 1. Solvent screening with Ir/3,3′di-Me-MonoPhos (**L2**) for the hydrogenation of **3** to **2**. Conditions: $[Ir(COD)Cl]_2$ (0.005 mmol), **L2** (0.02 mmol), **3** as the free base (0.2 mmol), solvent (5 mL), and H_2 (25 bar) at 50 °C for 16 h.

Scheme 4. Layout of A96 Reactor Screening and the Obtained ee's[a]

A1 = phthalimide
A2 = I_2

Ir 1 = $Ir(COD)_2BF_4$
Ir 2 = $[Ir(COD)Cl]_2$

L3 L4 L5: JosiPhos 009-1

additives

		none	A1	A2	none	A1	A2	none	A1	A2	none	A1	A2
Ir 1	L2	31	30	28	28	32	29	53	40	-11	20	25	17
	L3	-44	-41	-44	-28	-24	-27	-33	-27	-24	-26	-12	-47
	L4	1	1	-25	22	20	-22	31	31	-40	8	8	-26
	L5	17	16	1	3	3	1	3	4	0	1	43	1
Ir 2	L2	64	62	51	35	34	45	27	17	32	-2	-2	43
	L3	-56	-66	-49	-54	-55	-31	-57	-57	-26	-27	-27	-51
	L4	10	10	0	-2	-1	0	6	1	12	22	15	6
	L5	67	66	76	28	34	35	15	18	36	31	41	49
		EtOAc			MIBK			DCM			IPA		

solvents

100-90
90-80
80-70
70-60
60-50
50-40
40-30
30-20
20-10
10-0

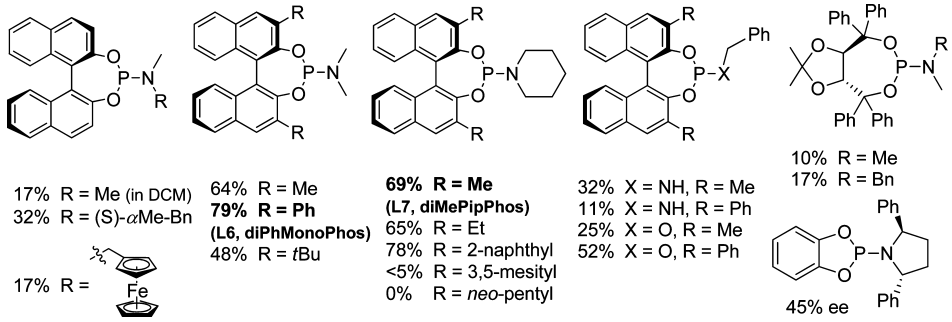
[a]Conditions: $[Ir(COD)Cl]_2$ (0.00055 mmol), ligand (1 or 2 equiv/Ir), **3** as the free base (0.03 mmol), solvent (1.5 mL), and H_2 (25 bar) at 50 °C for 16 h. Almost all of the conversions were above 90% and are not mentioned here for clarity.

increase the enantioselectivity. A large number of ligands were tested (Scheme 5), and the importance of the substitution at the 3- and 3′-positions of the binaphthol backbone was confirmed. In the absence of these substituents, the ee's were quite low. The same was true when very bulky groups such as *tert*-butyl, neopentyl, or mesityl were present at the 3- and 3′-positions. Phenyl substituents gave the best ee's (79%). On the other hand, no clear trends were found with the substitution pattern on the amino group. Taddol- or catechol-based phosphoramidites were also active but not particularly enantioselective.

Although the best enantiomeric excesses obtained with phosphoramidites remained modest, we decided to further optimize the catalytic system, anticipating that enantiomeric enrichment would occur upon crystallization of the product. Up until now, hydrogenation had been performed at low S:C ratios (i.e., between 25−200 mol:mol). However, decreasing the catalyst amount by more than 1 order of magnitude was still required to make the transformation cost-effective for large-scale production. Unfortunately, a strong decrease in activity and enantiomeric excess was observed at S:C ratios above 200. At S:C = 300, incomplete conversion and an enantiomeric excess of 44% was obtained with di-Ph-MonoPhos (**L6**) instead of 79% at S:C = 25. Similarly, upon use of 3,3′-di-MePipPhos (**L7**), the performance of the catalyst dropped from full conversion and 69% ee at S:C = 200 to 67% conversion and 48% ee at S:C = 500. Several explanations[17] are possible for this behavior, the most obvious one being the presence of an

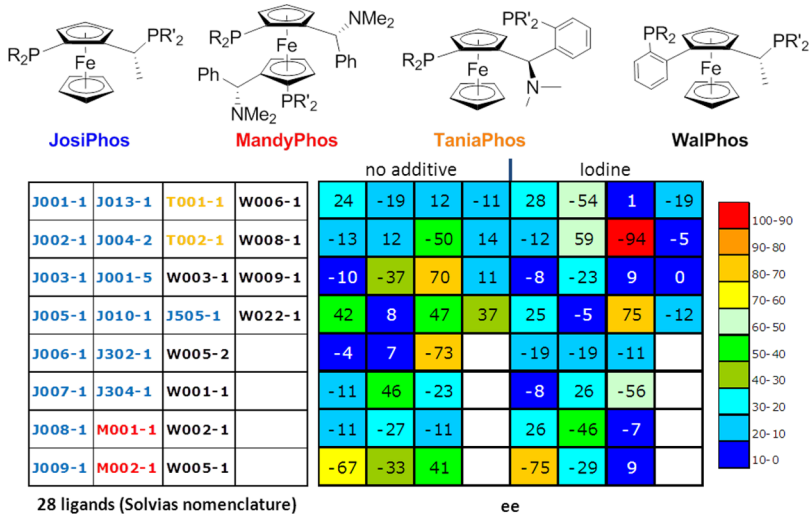
dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531−1539

Scheme 5. Enantiomeric Excesses (ee's) for Selected Examples of Phosphoramidite Ligands Tested in the Ir-Catalyzed Hydrogenation of 3[a]



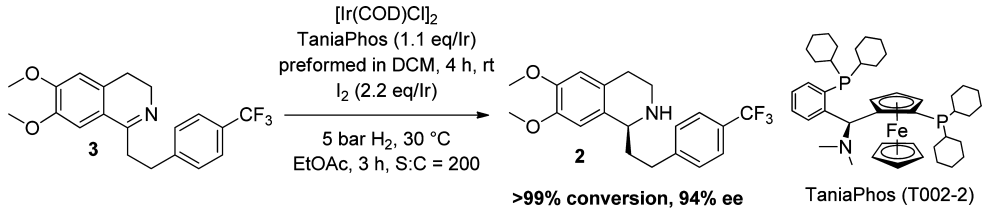
[a]Conditions: $[Ir(COD)Cl]_2$ (0.002 mmol), ligand (0.004 mmol), **3** as the free base (0.1−0.2 mmol, S:C = 25−50), EtOAc (5 mL), and H_2 (25 bar) at 50 °C for 2 h. Conversions are not shown but were >20% for all examples.

Scheme 6. Results of the Screening of 28 Ligands from the Solvias Collection[a]



[a]Conditions: $[Ir(COD)Cl]_2$ (0.00163 mmol), ligand (0.00326 mmol) (structures are shown in the Supporting Information), **3** as the free base (0.0326 mmol, S:C = 10), EtOAc (5 mL), and H_2 (25 bar) at 50 °C for 18 h. Conversion was >90% for all examples except for M002-1 (73%) (see the Supporting Information).

Scheme 7. Asymmetric Hydrogenation of 3 with Ir/TaniaPhos



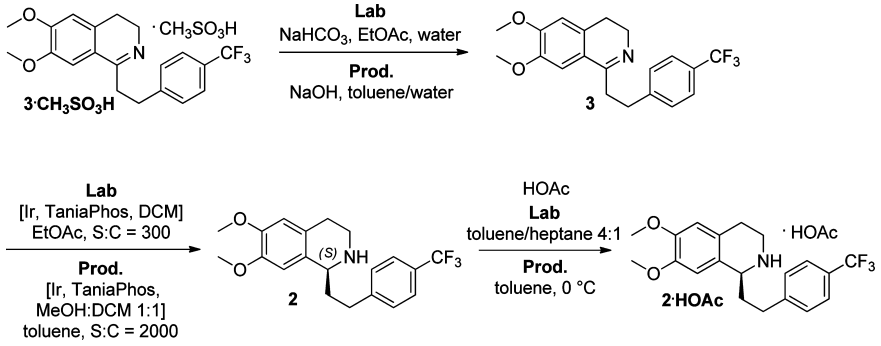
impurity in the substrate that acts as a poison for the catalyst. Another explanation is substrate and/or product inhibition. Increasing the S:C ratio favors the binding of the substrate and/or the product to the metal center. Eventually the chiral ligand is displaced, leading to the formation of inactive or non-enantioselective Ir species. Because phosphoramidites are monodentate ligands, their displacement by N-containing compounds may occur more readily than for bidentate ligands.

4. Further Improvement of the Ferrocene Lead. In contrast to phosphoramidites, the ferrocene ligand/Ir catalyst exhibited improved performance in the presence of iodine. Using the high-throughput screening platform, we tested another 28 ferrocenyl disphosphine ligands available in house with $[Ir(COD)Cl]_2$ as the precursor in EtOAc as a solvent with and without iodine as an activator (Scheme 6).

To our delight, one single ligand out of the whole series, TaniaPhos T002-1 (R = R′ = cyclohexyl) resulted in full conversion and the highest ee ever obtained in our hands (94%).[18] Although this was not the case for all of the ligands tested, the addition of I_2 was crucial to render the Ir/TaniaPhos combination highly enantioselective. The second-best results were obtained using JosiPhos-type ligands with or without iodine. Initially, the results were variable until we realized that this was caused by incomplete coordination of the ligand to the Ir precursor. When we performed the first catalyst preparation in the A96 reactor, we allowed for a long incubation time of the

dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531−1539

Scheme 8. Three-Step Process from 3·CH_3SO_3H to 2·HOAc As Performed in the Laboratory Phase (Lab) and in Production (Prod.)[a]



[a]The concentrations of **3·CH_3SO_3H** and **3** were 6.6 and 23% w/w in the lab and production, respectively. The concentration of the intermediate solution containing **3** was adjusted to 5 and 18% w/w in the lab and production, respectively.

Ir precursor with the chiral ligand (around 1 h) prior to the addition of iodine since 96 reaction mixtures had to be prepared in parallel. In our subsequent trials where we tested only the successful TaniaPhos, the time for formation of the precatalyst was shortened to 10−20 min. Surprisingly, the complexation was not complete under these conditions, and upon addition of I_2, active but non-enantioselective Ir species were formed, leading to a lower ee of the product. Hence, once the Ir precursor and the ligand were allowed to form the complex in DCM (at rt for 4 h, or at 40 °C for 30 min) prior to the addition of I_2, the results obtained in the A96 reaction (2.5 mL of solvent) were reproducible on a larger scale (70 mL of solvent) (Scheme 7).[19]

5. Scale-Up of Asymmetric Hydrogenation. For the pilot plant campaign (six batches of 45 kg) and the validation campaign (10 batches of 750 kg), a lab improvement program was initiated with the following targets. First, the number of solvents used in the process for the production of the desired HOAc salt of **2** should be reduced (see Scheme 8). In the lab experiments, four solvents (EtOAc, DCM, toluene, and heptane) had been used. Second, we wanted to reduce the amount of catalyst because of the high costs of Ir and TaniaPhos (target: S:C > 1500).

A first improvement was quickly made when we observed that the hydrogenation ran smoothly in toluene as the solvent (using the same conditions as in EtOAc). The next step was to verify whether efficient freebasing could be done in toluene. The imine salt **3·CH_3SO_3H** is less soluble in toluene than in EtOAc and more water had to be used. However, since a more concentrated solution of NaOH is compatible with toluene, the overall volume of liquids could be reduced, allowing a larger batch size (up to 23% w/w of free imine). More importantly, the solvent switch for the final crystallization of **2·HOAc** could be avoided since the hydrogenation was performed in toluene instead of EtOAc.

The next logical step was to test the preparation of the catalyst in toluene. Although the Ir/TaniaPhos complex is very soluble in toluene, a black precipitate formed immediately upon addition of the iodine. This solid was tested in the hydrogenation with toluene as the solvent, giving low conversion and ee. As already mentioned, the performance of the catalyst appeared to be dependent on its mode of preparation, and further investigations led to a significant reduction of the amount of catalyst. During a study performed by Solvias, it was discovered that preparing the catalyst in MeOH improved the activity of the catalyst up to S:C = 3000 without loss of ee and activity. The exact role of MeOH is not fully understood. It is assumed that it can coordinate to the Ir center and either favors its activation by I_2 and/or stabilizes the active species. Unfortunately, the catalytic system appeared to be very poorly soluble in MeOH. Therefore, the MeOH preparation could not be used for large-scale production. However, preparing the catalyst in a 1:1 DCM:MeOH mixture appeared to be a good compromise, as it combined the benefits of MeOH (albeit less than for pure MeOH) with good solubility. With this preparation method, an S:C ratio of 2000 was reached during the validation campaign. The hydrogenation in toluene also appeared to be much more tolerant to high substrate concentration. In EtOAc, increasing the concentration of free imine above 5.1% w/w led to a decrease in ee, while in toluene a concentration as high as 18% w/w could be used.

Finally, the final crystallization of the acetate salt of **2** could be efficiently done in toluene at 0 °C, thereby avoiding the use of heptane. Gratifyingly, enantiomeric enrichment from 91% ee to 99.8% ee occurred during the crystallization. Residual DCM and MeOH from the catalyst preparation had to be removed in order to maintain a high yield.

The proven acceptable range (PAR) study revealed the importance of several other parameters. The iodine to Ir ratio was ideally kept above 1.8. A lower amount led to lower conversion and ee. The TaniaPhos ligand to Ir ratio also had to be carefully controlled between 0.5 and 2.0. When the hydrogenation was performed at 0 °C, the reaction rate was about 4 times slower than at rt. On the other hand, at 35 °C, the enantiomeric excess dropped to 87%. Concerning the pressure, the reaction was effective at 3 bar. After conversion to the free base, the imine could be stored for a few days as a toluene solution. However, there was formation of some low-level byproducts that acted as poison for the catalyst, leading to a slight decrease in conversion of the hydrogenation at a similar S:C ratio (from 99% to 95% conversion after 4 days of storage). After 1 week of storage, the conversion was entirely inhibited, and no hydrogenated product was observed. The main solvent in the process is toluene. During the last step, the free amine **2** was precipitated as its acetate salt from the toluene solution upon addition of glacial acetic acid. Traces of HOAc have a very detrimental effect on the catalyst performance (low ee and conversion). For that reason, the recycling process of toluene involved an extraction with aqueous NaOH and water prior to

dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531−1539

Table 1. Details of the 10 Hydrogenation Batches with In-Process Control (IPC) by HPLC at Different Reaction Times and Chiral Purities of the Batches

batch	1	2	3	4	5	6	7	8	9	10
S:C	1200	1500	2000	2500	2000	2000	2000	2000	2000	2000
HPLC area of **2** (%)										
IPC 1 h	<0.1	0.6	20.4	36.8	25.0	7.1	7.0	17.1	1.4	2.0
IPC 2 h	–	–	1.2	6.0	2.0	1.0	0.7	1.7	1.0	1.0
IPC 3 h	–	–	0.8	2.0	0.7	0.7	0.5	–	0.7	0.5
IPC 4 h	–	–	–	2.0	–		–	1.1	–	–
chiral purity (% ee)	96.4	96.3	96.2	95.9	96.2	96.2	96.5	96.4	96.5	96.4

Scheme 9. Asymmetric Transfer Hydrogenation for the Production of 2

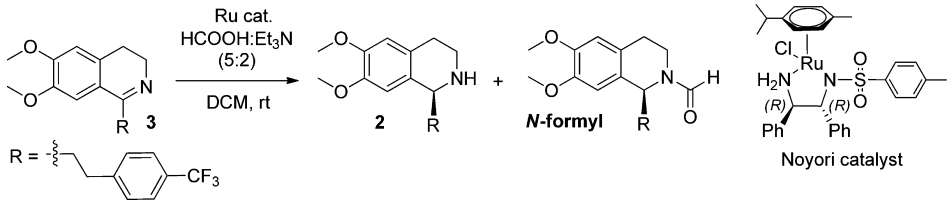


Table 2. Screening of Reaction Conditions in the Asymmetric Transfer Hydrogenation of 3 (or 3·CH_3SO_3H)[a]

entry	conditions	*T* (°C)	time (h)	conv. (%)	ee (%)	*N*-formyl (area %)
1	**3**, DCM, TEAF = 5:2 (5.8 equiv), S:C = 1000/1	23	42	100	85	13.3
2	**3·MsOH**, DCM, TEAF = 5:2 (5.8 equiv), S:C = 1000/1	23	22	100	91	2.1
3	**3·MsOH**, AcOEt, TEAF = 5:2 (5.8 equiv), S:C = 1000/1	23	40	100	86	6.3
4	**3·MsOH**, IPA, TEAF = 5:2 (5.8 equiv), S:C = 1000/1	23	65	73	87	2.4
5	**3·MsOH**, EtOH, TEAF = 5:2 (5.8 equiv), S:C = 1000/1	23	48	55	89	1.2
6	**3·MsOH**, DCM, TEAF = 5:2 (3 equiv), S:C = 2000/1, reflux	28	90	100	80	15.6
7	**3·MsOH**, DCM, TEAF = 1:1 (5.8 equiv), S:C = 1500/1, reflux	28	20	99	89	4.2
8	**3·MsOH**, DCM, TEAF = 1:1 (3 equiv), S:C = 2000/1, reflux	31	24	100	90	2.0

[a]The catalyst used for all experiments was (*p*-cymene)Ru(Cl)$_2$(Ts-DPEN), see Scheme 9, reaction performed on 9 g scale, reflux, 28−32 °C, p = 550 mbar. In the column "conditions", the parameter that is varied from one experiment to the other is underlined.

its reuse in hydrogenation. We found that up to 0.1% v/v of water could be tolerated in the hydrogenation process.

The validation campaign produced 6 t of the acetate salt of **2** in a total of 10 batches (see Table 1). The asymmetric hydrogenation was performed in a large-scale reactor loaded with 750 kg of the free amine under 6 bar H_2. Gradually, the S:C ratio was increased starting at 1200 for the first batch up to 2500 for the fourth batch. However, at this high S:C ratio, the reaction did not reach completion even after 4 h. Therefore, the remaining batches were run at S:C = 2000. The ee after the asymmetric hydrogenation step was routinely ∼96% across the campaign. After crystallization, all 10 batches met the specification. Starting from 7.6 mT of imine salt, 6 mT of the amine salt was produced (86% yield).

Although reasonably high S:C ratios were reached during the validation campaign, the cost of the catalyst, and more specifically of TaniaPhos, still represented a significant part of the total production cost. Therefore, it was decided to continue the search for a cheaper alternative. We turned towards asymmetric transfer hydrogenation with the goal of demonstrating the scalability of this transformation at high S:C ratios.

6. Screening for a Transfer Hydrogenation Catalyst. Confirming the results obtained earlier with a standard Noyori catalyst was rather straightforward (Scheme 9). The first experiment at S:C = 1000 immediately gave the desired product with full conversion and high ee (90%) after 18 h. The reducing agent used was a mixture of formic acid and triethylamine in the usual 5:2 azeotropic ratio as disclosed by Noyori.[3] However, on a slightly larger scale (9 g), the reaction became slower (full conversion after 40 h; Table 2, entry 1) and slightly less enantioselective (85% ee), but more worryingly, a side product that had been overlooked so far was detected by HPLC (13 area %) and identified as the *N*-formylated analogue of **2** (Scheme 9).

Reasoning that the mesylate salts of **2** and **3** would be less prone to react with formic acid, we decided to introduce a stoichiometric amount of CH_3SO_3H simply by undertaking the transfer hydrogenation reaction directly from the imine salt, **3·CH_3SO_3H** (i.e., without prior freebasing). The unknown was whether the imine salt would remain sufficiently active towards transfer hydrogenation and how much the presence of an additional acid would affect the enantioselectivity.[20] To our satisfaction, the reaction worked very well (Table 2, entry 2). Full conversion was retained within 22 h with only 2.1 area % for the *N*-formyl byproduct and an enantioselectivity of 91%. Since DCM is not the most preferred solvent for large-scale production, we performed a solvent screen (EtOAc, IPA, EtOH; entries 3−5), but none of those solvents outperformed DCM. In protic solvents, the formation of *N*-formylated **2** was minimal, but unfortunately, the reaction was not complete even after an extended time. The next step was to lower the amount of catalyst. At S:C = 2000, the reaction went to completion but required 3 days under reflux (entry 6), leading to a large amount of *N*-formylated byproduct. It became apparent that the key to limiting the formation of the byproduct was to accelerate the reaction. It is known that the activity of the

dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531−1539

Table 3. Comparison of the Two Catalytic Routes (AH and ATH) towards the Key Chiral Intermediate 2[a]

entry	parameter	AH		ATH	justifications
1	substrate	**3**	<	**3·CH_3SO_3H**	no need for freebasing in ATH
2	catalyst	Ir/TaniaPhos	<	Ru-Noyori	Ru cheaper than Ir, ATH ligand much cheaper
3	operating conditions	S:C = 1500, 16−18 °C, 6 bar H_2	=	S:C = 1500, 28−32 °C, 550 mbar	rated equally
4	reactor technology	H_2 infrastructure and pressure reactor	<	standard reactor	ATH allows for more flexibility in multipurpose assets
5	reaction time batch time cycle time	10 h 97 h 18 h	>	32 h 115 h 44 h	long reaction time with Ru cat slows down throughput by a factor of 2
6	relative concentration (kg of product/m^3)	1.0	<	1.4	ATH can be run at higher concentrations
7	solvents	toluene, heptane	>	DCM, toluene	ATH requires one solvent switch and utilizes DCM
8	solution ee	96%	>	89%	
9	PMI[24]	22 (15 without H_2O)	<	27 (21 without H_2O)	
10	relative variable cost/kg	1.0	>	0.65	economically attractive ATH catalyst system
11	relative fixed cost/kg	1.0	=	0.98	ATH is slower but run at higher concentration and less equipment needed; effects are balanced

[a]Entries 6, 10, and 11 have been normalized for the asymmetric hydrogenation (AH) process.

catalyst in transfer hydrogenation can vary significantly with the pH (i.e., with the HCOOH:Et_3N ratio).[21] Using 1:1 TEAF (entry 7), we indeed observed that the reaction occurred much faster and, as expected, with a lower amount of side product. Finally, by using a smaller excess of TEAF (entry 8), we could perform the reaction at S:C = 2000 with an acceptable level of byproduct that could be removed during workup.

The cleavage of the formyl group of the side product by base or acid was not successful. Treatment with diluted bases or acids showed no reaction, while strong acids or bases led to decomposition. Extraction of **2** into an aqueous phase as its acetate salt while leaving the *N*-formyl side product in the organic phase appeared to be a good strategy. The *N*-formylated **2** was depleted to ca. 1 area %. However, even better was the direct crystallization of **2·HOAc** after a solvent switch to 4:1 toluene/heptane. In this case, the amount of *N*-formyl side product was 0.2−0.6 area %.

7. Scale-Up of the Transfer Hydrogenation. This process was used to produce two batches of 18 and 12 kg. Both batches were run in a large-scale Hastelloy reactor at S:C = 1500. The reaction was maintained under reflux between 28 and 32 °C at 550 mbar for 8 h. This allowed the efficient removal of CO_2 and therefore avoided its conversion to CO, which would act as a poison for the catalyst.[22] The two batches performed equally well (89.7% ee and 89.4% ee, respectively). After a solvent switch, the crystallization of the acetate salt of **2** was performed in toluene. Starting from 18 kg of **3·CH_3SO_3H**, 14.5 kg of **2·HOAc** was produced with a yield of 87%. Another larger pilot campaign was run with 5 batches resulting in several hundreds of kilograms of **2**.[23]

8. Comparison of the Hydrogenation and Transfer Hydrogenation Processes. Although our study of the asymmetric transfer hydrogenation route was still ongoing, it was sufficiently advanced to allow for a fair comparison of the two routes. Table 3 summarizes the main features of both technologies, highlighting their specific advantages. Both processes have pros and cons. In the transfer hydrogenation process, the imine salt **3·CH_3SO_3H** can be used as a substrate, thereby avoiding the freebasing step (entry 1). Although the process based on transfer hydrogenation is slower than the one based on hydrogenation (entry 5), the fixed costs of the two processes are identical because higher concentrations can be used with ATH. From an ecological and environmental point of view, the hydrogenation technology is slightly better, as indicated by the calculated process mass intensity (PMI)[24] (entry 9). From an economic standpoint, the Noyori process is more favorable because of the overall lower costs of goods, mainly driven by the catalyst price (entries 2 and 10). For both processes, the reaction conditions are mild and well within an acceptable range for production (entry 3), although ATH offers more flexibility as it can be carried out in any standard reactor (entry 4).

■ CONCLUSION

Via catalyst screening on a lab scale, we discovered two efficient catalytic systems for the enantioselective synthesis of the intermediate **2·HOAc** towards almorexant, one relying on asymmetric hydrogenation using an Ir complex with a ferrocene-based ligand and the other one relying on asymmetric transfer hydrogenation using a Ru catalyst with a diamine ligand. Both catalysts were studied further and appeared to be suited for large-scale manufacturing. In case the production had continued,[23] a final choice would have been guided mainly by the cost of goods for the two routes, considering the availability of the production units and the delivery time of the raw materials.

■ EXPERIMENTAL SECTION

(*S*)-6,7-Dimethoxy-1-(4-(trifluoromethyl)phenethyl)-1,2,3,4-tetrahydroisoquinoline Acetate (**2·HOAc**).

Hydrogenation on a Production Scale. *Freebasing.* A large-scale reactor was charged with toluene (2600 kg) and purified water (1200 kg). **3·CH_3SO_3H** (750 kg, 1.63 kmol) was added, followed by 50% NaOH (160 kg). The mixture was stirred for 1 h. After phase separation, the lower phase was removed, and the organic phase was washed with purified water (3 × 1000 kg). Water present in the organic phase was removed by azeotropic distillation. The solution was transferred into the 6.3 m^3 hydrogenation reactor.

Precatalyst Preparation. A reactor was charged with MeOH (3.2 L) followed by I_2 (0.413 kg, 1.63 mol). A second reactor was charged with $[Ir(COD)Cl]_2$ (0.257 kg, 0.38 mol), TaniaPhos (0.58 kg, 0.815 mol), DCM (22 L), and MeOH (32 L). The mixture was stirred for 3 h at rt, after which time

dx.doi.org/10.1021/op400268f | Org. Process Res. Dev. 2013, 17, 1531−1539

the I_2 solution was added. The mixture was stirred for 30 min and then transferred to the hydrogenation reactor.

Hydrogenation. The reactor was pressurized with H_2 (6 bar min.) without stirring, and the pressure was released. The reactor was again pressurized to 6 bar H_2, and the stirrer was started. The temperature was maintained between 16 and 18 °C. When the starting material was depleted to less than 2.0% a/a (HPLC analysis), the reaction was stopped.

Crystallization. A fraction of the reaction solvent was removed by distillation under low pressure. Additional toluene was added to adjust the concentration of **2** to between 7.8 and 9% (w/w). Acetic acid (98 kg, 1.63 kmol) was slowly dosed while maintaining the temperature at 20 °C. The mixture was stirred for 30 min. After filtration and drying, the final product was packed into 40 kg drums. Overall yield of **2·HOAc**: 86%, >96% ee. ^{1}H and ^{13}C NMR data corresponded to those in the literature.[1a]

Transfer Hydrogenation on a Production Scale. A large-scale reactor was charged with **3·CH_3SO_3H** (18 kg, 39.17 mol), DCM (59.9 kg), and formic acid (5.4 kg, 117.3 mol). The solution was cooled to 0−10 °C, and Et_3N (11.88 kg, 117.4 mol) was slowly added while maintaining the temperature below 15 °C. The solution was heated to 20−25 °C, stirred for 1 h, and further heated to 30−32 °C. The batch was brought to reflux at this temperature by applying vacuum (∼550 mbar) and kept refluxing for 10 min before the catalyst, (chloro)-{[(1*R*,2*R*)-(−)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)-amido}(*p*-cymene)ruthenium(II), was added [17 g, 26.7 mmol dissolved in degassed DCM (0.5 L)]. The reaction was continued until the amount of starting material was less than 2.0% a/a (89.7% ee). The reactor was vented, and additional DCM was added to compensate for the loss occurring during the reaction. The batch was cooled to 20−25 °C and diluted with DCM (29.9 kg). The resulting solution was washed with water (28.1 kg), saturated aqueous $NaHCO_3$ (43.7 kg), and water (15.8 kg). The organic phase was concentrated to 27 L by distilling off the solvent at 40−50 °C. Toluene (48.2 kg) was added, and the batch was concentrated again by distillation (final volume 27 L). Another portion of toluene (108 kg) was added. Sampling for IPC showed DCM < 0.5% w/w, concentration of **2** = 9.5−11.5% w/w, ee >85%. At 20−25 °C, HOAc (2.23 kg, 37.14 mol) was added. The resulting suspension was stirred for 1 h at 20 °C and for 1 h at 0 °C. The product was isolated by centrifugation and rinsed with toluene (19.8 kg). The damp product was deliquored under a stream of N_2 and dried under reduced pressure at 40 °C until the toluene content was below 1.8% w/w. Overall yield of **2·HOAc**: 87%, 99.7% ee. ^{1}H and ^{13}C NMR data corresponded to those in the literature.[1a]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Analytical methods and the procedure for the catalyst screening. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ ACKNOWLEDGMENTS

We thank our colleague Math Boesten from the analytical group for his invaluable support in HPLC method development. S.A. is indebted to Dr. Thomas Weller for constant support and fruitful input. C.I., J.S., and S.A. thank Dr. Erhard Bappert and Dr. Felix Spindler (Solvias AG) for their work on the optimization of the AH conditions.[25]

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