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Application of Crabtree/Pfaltz-type iridium complexes for the catalyzed asymmetric hydrogenation of an agrochemical building block

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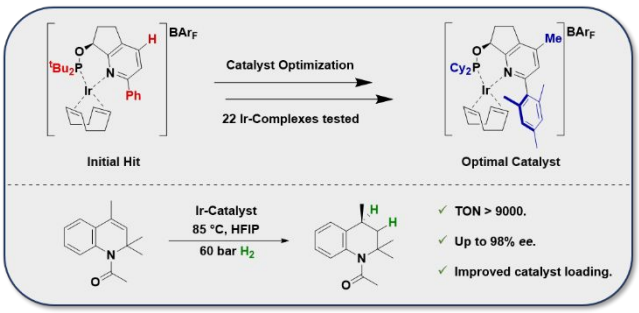
Table of Content (TOC) Graphic

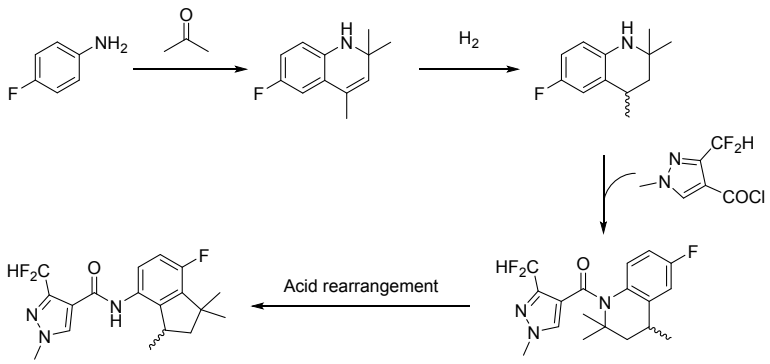


Abstract: Herein we report improved chemo- and enantioselective hydrogenations of 1-(2,2,4-trimethylquinolin-1(2*H*)-yl)ethan-1-one (**1**) towards (*R*)-1-(2,2,4-trimethyl-3,4-dihydroquinolin-1(2*H*)-yl)ethan-1-one (**2**) using well-defined novel Crabtree-type iridium complexes.

Keywords: Asymmetric hydrogenation; Alkene reduction; Catalyst design; Iridium catalysis, Unactivated olefins; *N*-heterocycles

Aminoindanes are important building blocks for the synthesis of aminoindane amides, which were disclosed to be active compounds for the control of phytopathogenic fungi (Scheme 1).[1] First protocols for the preparation of this class of compounds were reported in 1985 by the Sumitomo Chemical Company.[2] Since then, the majority of commercially available fungicides of this type were used as racemic mixtures. Since the individual enantiomers usually have a different performance, an enantioselective synthesis is highly desirable for efficiency and sustainability. Thus, first attempts to isolate enantiomerically pure building blocks used crystallization of a diastereomeric salts with D-tartaric acid.[3]

Scheme 1. Selected example for the synthesis of an aminoindane amide fungicide.[4]



However, the asymmetric hydrogenation of 1-(2,2,4-trimethylquinolin-1(2*H*)-yl)ethan-1-one would represent a much more elegant solution, as it offers advantageous features

such as excellent atom-economy and quantitative yields as well as high levels of stereoselectivity. Following this approach, a selective hydrogenation of the non-functionalized tri-substituted alkene moiety has to be achieved. The selective hydrogenation of such types of double bonds is still challenging and best results are typically obtained applying chiral Crabtree/Pfaltz-type iridium complexes.[5] Previously, it was discovered that by replacing the established hexafluorophosphate anion with the weakly coordinating BAr_F^- anion enabled not only the use of catalyst loadings lower than 1 mol% but also provided a catalytic system less sensitive to moisture.[6] Impressive examples for the asymmetric hydrogenation using these complexes were the hydrogenation of γ-tocotrienyl acetate,[7] and the total synthesis of dimethyl methoxycalamenene.[8] Unfortunately, utilizing 1.25 mol% of the commercially available complex [Ir(COD)ThrePHOX]BAr_F for the asymmetric hydrogenation of **1** to **2** resulted only in 14% conversion and low enantioselectivity (31% *ee*) (Figure 1).[9] Clearly, from an industrial point of view, neither the activity nor the selectivity is suitable for any application. In order to justify the use of an expensive iridium precursor, a lower catalyst loading and a higher selectivity have to be achieved.

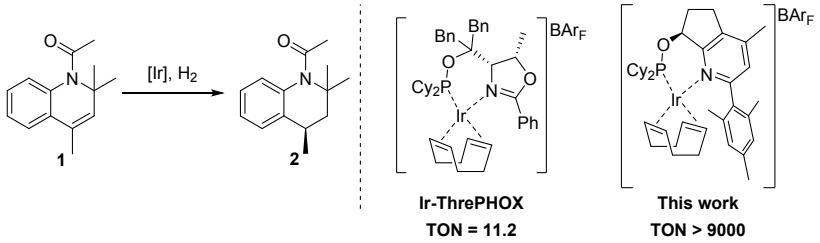


Figure 1. Crabtree/Pfaltz-type iridium complexes for the desired transformation.

Here, we report a state-of-the-art process for this transformation, which allows for the first time a practical and industrial feasible synthesis of **2** and related building blocks via asymmetric hydrogenation.

Results and Discussion

A preliminary catalyst screening using commercially available and tailor-made iridium complexes revealed complex **5a** as a benchmark catalyst (Figure 2).[10] Notably, this type of ligand was originally introduced by Pfaltz and co-workers for asymmetric hydrogenation of olefins and furane derivatives.[11]

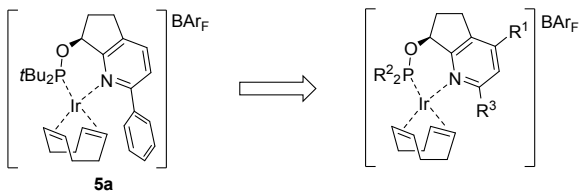
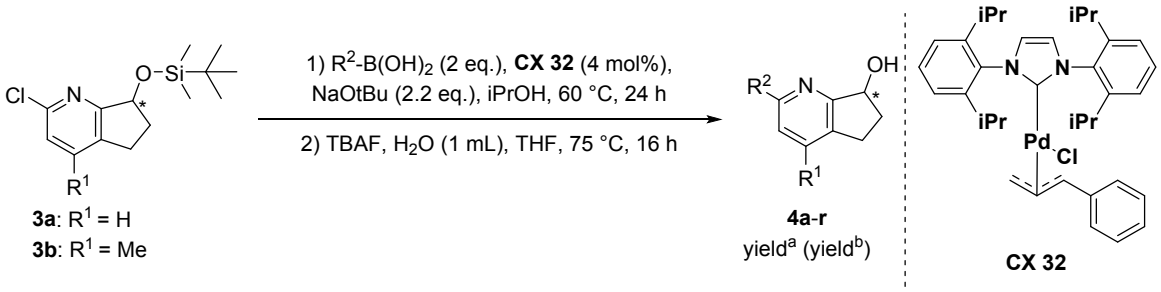
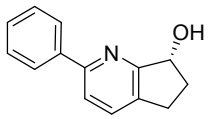


Figure 2. Benchmark catalyst for the hydrogenation of **1**.

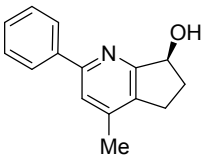
Initially, we started to investigate the influence of different substituents of **5a** (indicated by the R groups in Figure 2). Following the protocol by Pfaltz and co-workers, we started synthesizing chiral pyridyl alcohols using the building blocks (*R*)-7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (**3a**) and (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-2-chloro-4-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (**3b**) (Scheme 2).[12] Eighteen different pyridyl alcohols were obtained overall in moderate to good yields (**4a**-**r**) from the Suzuki reaction of **3a** or **3b** with the corresponding boronic acids, followed by deprotection of the silyl ether.

Scheme 2. Synthesis of chiral pyridyl alcohols.

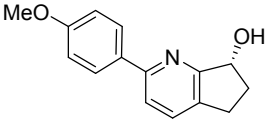




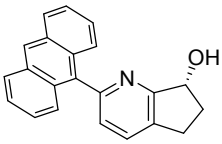
4a
79% (86%)



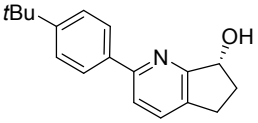
4b
75% (82%)



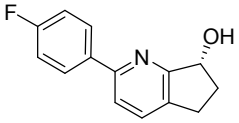
4c
71% (84%)



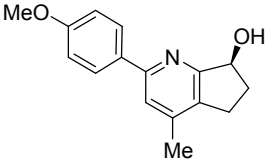
4d
19% (43%)



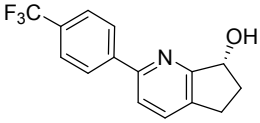
4e
63% (80%)



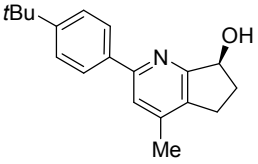
4f
65% (77%)



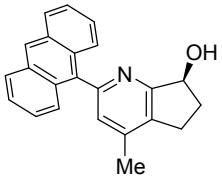
4g
77% (82%)



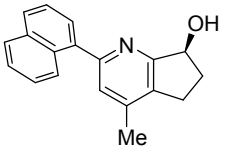
4h
76% (80%)



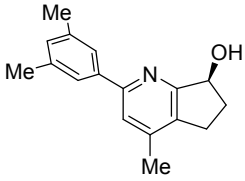
4i
48% (57%)



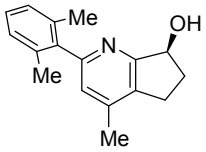
4j
46% (n.d.)



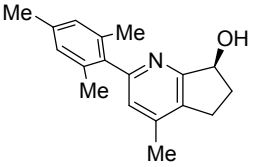
4k
82% (85%)



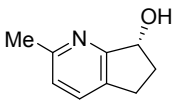
4l
25% (51%)



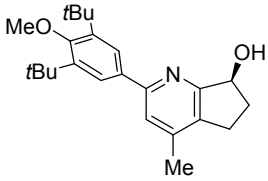
4m[c]
68% (82%)



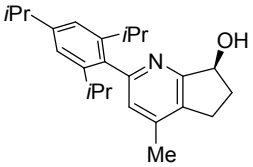
4n[c]
79% (86%)



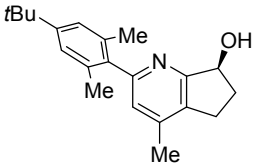
4o[d]
81% (95%)



4p
51% (69%)



4q[e]
58% (66%)



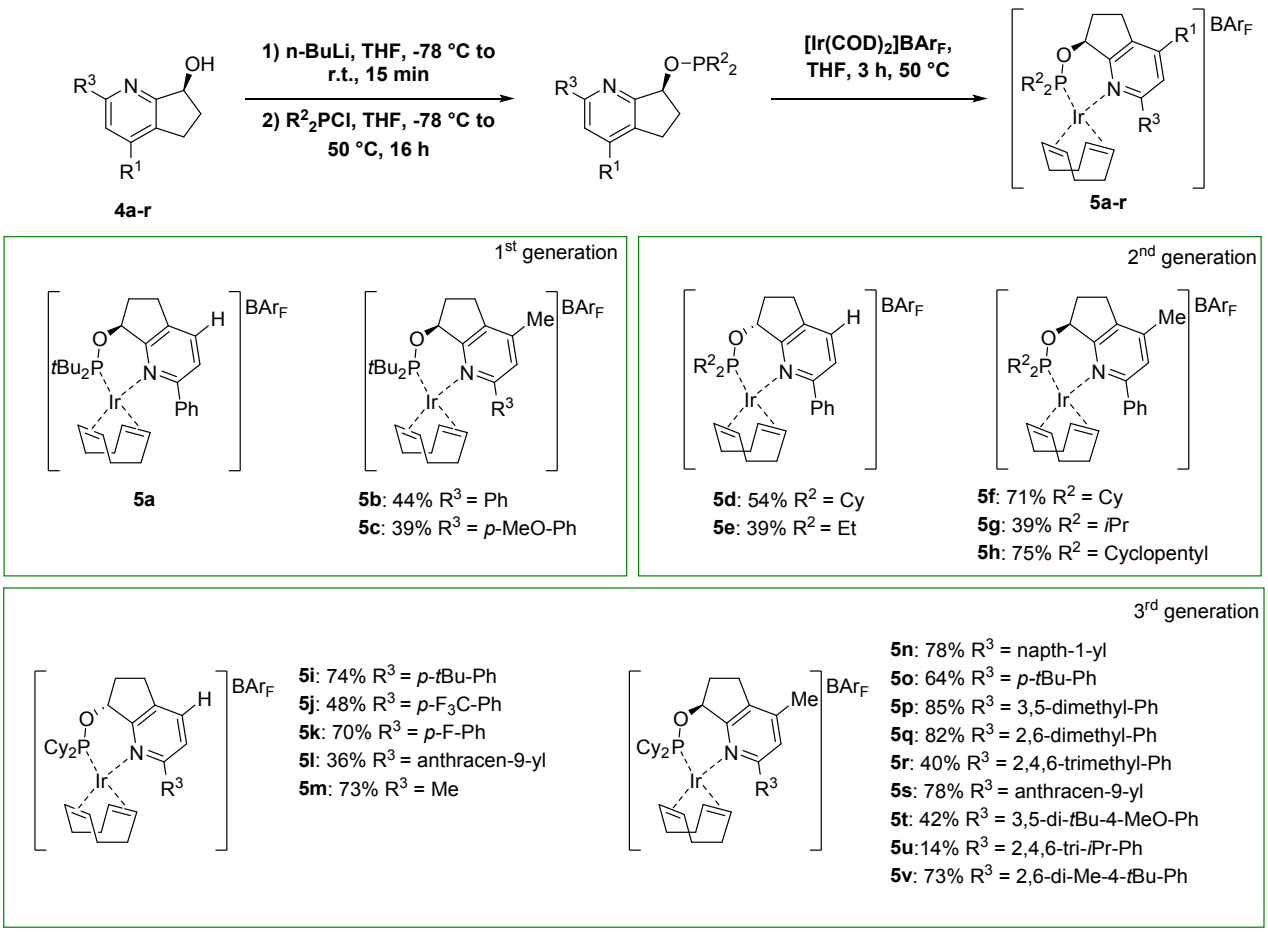
4r[c]
70% (85%)

[a] Isolated yield over two steps. [b] Isolated yield of the Suzuki reaction is given. [c] **3b** (2 mmol), boronic acid (2.3 mmol), **CX 32** (2 mol%), NaOH, *i*-PrOH, H_2O, 115 °C, 48 h. [d] **3a**

(2 mmol), trimethylboroxine (1.5 eq.), (dppf)$PdCl_2$·DCM (5 mol%), K_2CO_3 (3 eq.), 1,4-dioxane, 120 °C, 20 h. [e] **3b** (1 mmol), (2,4,6-triisopropylphenyl)boronic acid (1.2 eq.), $Pd(PPh_3)_4$ (15 mol%), K_3PO_4 (5.0 eq.), H_2O (1.0 mL), DME (5.0 mL), 110 °C, 24 h.

For the majority of the boronic acids [1,3-bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidene]chloro][3-phenylallyl]palladium(II) (**CX 32**) was found to be a suitable pre-catalyst for the coupling step. However, for highly bulky boronic acids higher temperatures and longer reaction times (**4m**, **4n** and **4r**) or even other palladium precursors ((dppf)$PdCl_2$·DCM, **4o** or $Pd(PPh_3)_4$, **4q**) were necessary in order to obtain decent product yields. Next, using these pyridyl alcohols, 22 different bench-stable iridium pre-catalysts were synthesized via the corresponding phosphonites (Scheme 3).

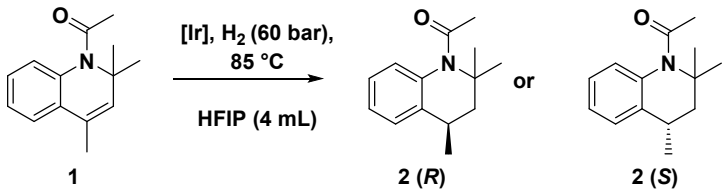
Scheme 3. Synthesis of iridium precatalysts.



Then, we investigated the effect of the different pre-catalysts in the benchmark hydrogenation of **1** (60 bar H_2, 85 °C, 6-40 h, HFIP, 0.1-0.01 mol% Ir). In order to get a fast insight into the catalytic behavior of the pre-catalysts and to avoid single hydrogenation reactions, all experiments were performed in a six-fold parallel manner (see SI). To our delight, in this "1st generation" screening a positive influence on the reaction outcome was obtained by replacing the proton in four position (R^1) of the pyridine moiety with a methyl group (**5a** vs. **5b**, Table 1, entries 2, 3). This observation was also

confirmed by later examples (**5d** vs. **5f** and **5l** vs. **5s**, Table 1, entries 6, 8, 15, 22). Next, a set of complexes were synthesized in order to elucidate the influence of R^2 groups on the phosphorus atom (Scheme 3, "2nd generation"). Since aryl-substituted phosphinites showed poor activity, we focused on alkyl phosphonites. Gratifyingly, when replacing the *tert*-butyl groups on the phosphorus atom with cyclohexyl groups, an increased activity and high enantioselectivity was observed (**5b** vs. **5f**, Table 1, entries 4, 8) at low catalyst loading (0.05 mol%). This result is in contrast to previous work by Pfaltz and co-workers, using similar type of ligands for the hydrogenation of (*E*)-2-(4-methoxyphenyl)-2-butene. Here, usually the *tert*-butyl substituted complexes gave significantly higher enantioselectivities compared to the cyclohexyl-substituted ones.[11a] Inspired by the work of Woodmansee *et al.*,[11b] we synthesized further complexes with less sterically demanding alkyl groups on the phosphorus atom.[13] However, the resulting complexes were less active and also less selective compared to **5f** (**5e**, **5g** and **5h**, Table 1, entries 7, 9, 10).

Table 1. Hydrogenation results of **1**.[a,b]



1 2 (*R*) 2 (*S*)

Entry	Complex	Time [h]	Loading [mol%]	Conv. [%]	TON	*ee* [%]
1	**5a**	16	0.1	99.2	992	98.0 (*R*)
2	**5a**	6	0.1	81.5	815	97.5 (*R*)
3	**5b**	6	0.1	94.5	945	97.5 (*R*)
4	**5b**	16.5	0.05	86.8	1736	97.6 (*R*)
5	**5c**	6	0.1	91.2	912	97.0 (*R*)
6	**5d**	16.5	0.05	88.2	1764	97.6 (*S*)
7	**5e**	16	0.1	30	300	90.0 (*S*)
8	**5f**	16.5	0.05	94.4	1888	97.3 (*R*)
9	**5g**	6	0.1	76.0	760	96.0 (*R*)
10	**5h**	16.5	0.05	87.9	1758	95.8 (*R*)
11	**5i**	16.5	0.05	98.4	1968	96.8 (*S*)

12	**5i**	16	0.025	67.2	2688	97.3 (*S*)
13	**5j**	16.5	0.05	34.6	692	83.2 (*S*)
14	**5k**	16.5	0.05	64.7	1294	92.4 (*S*)
15	**5l**	16.5	0.05	98.9	1978	95.8 (*S*)
16	**5l**	16	0.025	79.5	3180	97.5 (*S*)
17	**5n**	16.5	0.05	92.4	1848	96.9 (*R*)
18	**5o**	16	0.025	91.6	3664	97.3 (*R*)
19	**5p**	16	0.025	42.2	1688	94.5 (*R*)
20	**5q**	16	0.025	81.7	3268	97.9 (*R*)
21	**5r**	16	0.025	98.0	3920	98.1 (*R*)
22	**5s**	16	0.025	94.1	3764	97.5 (*R*)
23	**5m**	16	0.025	7.2	288	70.8 (*S*)
24	**5t**	16	0.025	60.0	2400	92.1 (*R*)
25	**5u**	16	0.025	74.0	2960	98.0 (*R*)
26	**5v**	16	0.025	97.5	390	97.3 (*R*)
27[c]	**5r**	40	0.01	93.9	9390	98.0 (*R*)

28[d]	**5r**	40	0.01	93.4	9340	97.6 (*R*)

[a] In general, only the lowest tested catalyst loadings for each complex are presented. [b] Standard reaction conditions: **1** (3 mmol), [Ir], HFIP (4 mL), H_2 (60 bar), 85 °C. [c] 12 mmol scale, 16 mL HFIP. [d] 25 mmol scale, 33 mL HFIP.

From the evaluation of complexes **5i-v** in the benchmark reaction (Scheme 3, "3rd generation"), some interesting trends were found: Electron-withdrawing groups, such as fluoro or trifluoromethyl, in the *para* position of the phenyl moiety lowered the activity as well as the selectivity dramatically (**5j** and **5k** vs. **5d**, Table 1, entries 6, 13, 14). Interestingly, previous work by Zhou's group did not show a similar trend in activity.[14] Replacing the phenyl group in position two of **5d** with an anthracenyl group led to a more active catalyst (**5l**), which gave nearly full conversion working with 0.05 mol% catalyst loading and still good conversion of 79.5% when 0.025 mol% was used. The naphthyl-substituted analogue (**5n**), however, was slightly less active than its phenyl-substituted counter-part (**5f**, Table 1, entries 8, 17). As expected, **5s** was more active than **5l**, giving a very good conversion of 94.1% at 0.025 mol% catalyst loading (Table 1, entry 22). While the methoxy-substituted complex **5c** was less active than **5b** (Table 1, entries 3, 5), the

p-tert-butyl-substituted derivative **5o** was more active compared to **5f** , providing the product in 91.4% yield (Table 1, entry 18). Encouraged by the results achieved with **5o**, we synthesized the complexes **5p-r** using the corresponding commercially available boronic acids. While **5p** and **5q** had a lower performance than **5o** (Table 1, entries 19, 20), **5r** gave 98% conversion at 0.025 mol% catalyst loading (Table 1, entry 21). Further increasing the steric demand of the ligand either led to a catalytically less active system (**5u**, Table 1, entry 25) or to an equally active catalytic system (**5v**, Table 1, entry 25). The motive in complex **5t**, which was used before by Pfaltz' group,[11b] gave only poor results for the desired reaction. As **5r** gave higher yield and selectivity compared to **5v**, we continued working with this complex. Notably, using only 0.01 mol% of **5r** was sufficient to give 93.9% of the product with an *ee* of 98% (*R*). This reaction could furthermore successfully be scaled-up to 25 mmol, yielding 93.4% of **2** with an excellent *ee* of 97.6%.

Conclusion

In conclusion, we synthesized and tested 22 different chiral iridium complexes for the hydrogenation of **1** to **2**, which is of general interest for the preparation of novel

agrochemicals. In the presence of the optimal iridium catalyst **5r** this transformation proceeds with high efficiency (TON >9300) and (enantio)selectivity (*ee* values up to 98%), so that industrially viable catalyst loadings can be achieved.

Experimental Procedures

General experimental procedure: The Ir-complex (catalyst loading given) and the substrate (3 mmol) were placed in an 8-mL autoclave vial containing a PTFE-coated stirring bar. The autoclave vial was closed using a screw cap with septum, placed in a fitted metal plate, connected to a Schlenk line and subsequently flushed with argon (10 min). HFIP (4 mL) was added via the septum to the vial. The vial was placed in an argon containing autoclave and the autoclave was flushed with argon (10 min). The autoclave was pressurized with hydrogen gas (10 bar) and subsequently depressurized to atmospheric pressure three times. After this the autoclave was pressurized to 60 bar hydrogen pressure and was placed in a suitable alumina block. After heating to 85 °C (~4°C/min; 15 min) the reaction was kept at this temperature for the given time. The autoclave was placed in an ice bath to allow fast cooling to room temperature. After

depressurizing, the vial was taken out of the autoclave and the reactions outcome was determined by GC-FID analysis (diluted with EtOH) and the enantiomeric excess by HPLC analysis.

General experimental procedure for up-scaling experiment (12 mmol): Complex **5r** (0.01 mol%) and the substrate (12 mmol) were placed in an 25-mL autoclave containing a PTFE-coated stirring bar and dissolved in hexafluoroisopropanol (16 mL). The autoclave was closed, flushed with Ar for 10 minutes and subsequently pressurized with hydrogen gas (10 bar) and depressurized to atmospheric pressure (three times). After this the autoclave was pressurized to 60 bar hydrogen pressure and was placed in a suitable alumina block. After heating to 85 °C (~4 $^{\circ C}/_{min}$; 15 min) the reaction was kept at this temperature for the given time. The autoclave was placed in an ice bath to allow fast cooling to room temperature. After depressurizing, the reactions outcome was determined by GC-FID analysis (diluted with EtOH) and the enantiomeric excess by HPLC analysis.

General experimental procedure for up-scaling experiment (25 mmol): Complex **5r** (0.01 mol%) and the substrate (25 mmol) were placed in an 50-mL autoclave containing

a PTFE-coated stirring bar and dissolved in hexafluoroisopropanol (33 mL). The autoclave was closed, flushed with Ar for 10 minutes and subsequently pressurized with hydrogen gas (10 bar) and depressurized to atmospheric pressure (three times). After this the autoclave was pressurized to 60 bar hydrogen pressure and was placed in a suitable alumina block. After heating to 85 °C (~4 $^{\circ C}/_{min}$; 15 min) the reaction was kept at this temperature for the given time. The autoclave was placed in an ice bath to allow fast cooling to room temperature. After depressurizing, the reactions outcome was determined by GC-FID analysis (diluted with EtOH) and the enantiomeric excess by HPLC analysis.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, NMR data TBS protected pyridyl alcohols, NMR data of deprotected pyridyl alcohols, NMR data of synthesized Ir-complexes, HR-MS data synthesized Ir-complexes, results of deuterium experiments, experimental procedures for catalytic tests.

Author Contributions

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ABBREVIATIONS

HFIP = 1,1,1,3,3,3-hexafluoro-propan-2-ol

BAr_F = Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

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