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Iridium-Catalyzed Asymmetric Hydrogenation of Substituted Pyridines

Alban Cadu,[b] Puspesh K. Upadhyay,[a] and Pher G. Andersson*[a, c]

Abstract: Asymmetric hydrogenation of *ortho*-substituted pyridines catalyzed by N,P-ligated iridium is demonstrated. To facilitate this reaction, the aromaticity of the pyridines was weakened by forming *N*-iminopyridium ylides. The reactions give very high conversions, and after a single recrystallization, excellent *ee* of up to 98% was obtained. This method lends itself to the synthesis of chiral piperidine building blocks.

Keywords: hydrogenation · iridium · *N*-iminopyridium ylides · pyridines · selective catalysis

Introduction

Chiral heterocycles are found in most fields of organic chemistry, from fragrances to pharmaceuticals.[1] Chiral piperidines are abundant in natural products and are found in a large number of biologically active natural products and drug molecules.[2] As such, methods to synthesize chiral heterocycles are of great value to synthetic chemists and have been an active research topic for over two decades.[3] Pyridines are cheap and commercially available starting materials, and constitute good precursors to piperidines through reduction. The use of transition-metal catalysts with gaseous hydrogen has become widespread in both heterogeneous and homogeneous catalysis, because of its high efficiency.[4] More recently, homogeneous iridium-catalyzed asymmetric hydrogenation allows, through excellent enantioselectivity and atom economy, the efficient synthesis of chiral compounds, especially building blocks.[5]

After Pfaltz and co-workers' development of a chiral analogue of Crabtree's catalyst, methods of iridium-catalyzed asymmetric hydrogenation were developed extensively.[6] These new catalysts were obtained by replacing the previously used PF_6^- counter-ion with $[BArF]^-$ (tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate) and the two monodentate ligands by the chiral, bidentate PHOX-ligand (phosphine-oxazoline). These catalysts are able to reduce many olefins, in excellent enantioselectivities and conversion, which had proved problematic in prior to this. Catalysts of the type [(N,P)Ir(cod)][BArF] (cod = 1,5-cyclooctadiene) were initially developed to hydrogenate very weakly coordinating alkenes;[6a,7] however, their use has been greatly expanded to include functionalized olefins.[8,9] The use of iridium catalysts offers a great advantage over rhodium and ruthenium because the coordination of the olefin takes place through a monodentate binding of the substrate through its olefinic bond to the iridium.[5a,9] In comparison, the rhodium and ruthenium normally transfer the chirality of their ligands to the substrate, in high enantioselectivity, if the substrate binds in a bidentate manner through both the olefinic bond and the coordinating group (often a carbonyl).[5b,10]

A number of catalytic methods and systems have been developed to synthesize chiral substituted piperidines. Recently Verendel et al. hydrogenated 3- and 4-substituted azacycles employing N,P-ligated iridium catalysts with excellent selectivity (up to >99% *ee*).[7a] The centers of chirality were located in these cases in the β or γ positions of the piperidines.[11] A similar substrate (unsaturated carboxylate-bearing piperidine) was hydrogenated with moderate success (60% *ee*) by using a palladium complex.[12] The use of rhodium and ruthenium to hydrogenate carboxylated azacycloalkenes has been reported to generate both piperidines and piperazines in very high selectivity.[13] However these methods for synthesizing unsaturated azacycles require lengthy multistep synthesis, whereas pyridines are cheap and available in large numbers of substitution patterns.

Although some aromatic rings have been hydrogenated very successfully,[14] pyridines remain challenging because of their stability to reduction and the amines' ability to bind competitively to the catalyst. Quinolines and isoquinolines have been hydrogenated with excellent results,[15,16] Pyridines require activation, normally by *N*-substitution to enable their successful hydrogenation. In a recent example, Zhou and co-workers reduced pyridiniumium salts by using iridium-Synphos as a catalyst.[17] The most successful use of N,P-ligated iridium for the asymmetric hydrogenation of pyridines was conducted by Legault and Charette,[18] who

[a] Dr. P. K. Upadhyay, Prof. Dr. P. G. Andersson
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, SE-10691 Stockholm (Sweden)
E-mail: phera@organ.su.se

[b] A. Cadu
Department of Chemistry-BMC
Uppsala University, Box 576, SE-75123 Uppsala (Sweden)

[c] Prof. Dr. P. G. Andersson
School of Chemistry and Physics
University of KwaZulu-Natal, Durban 4000 (South Africa)

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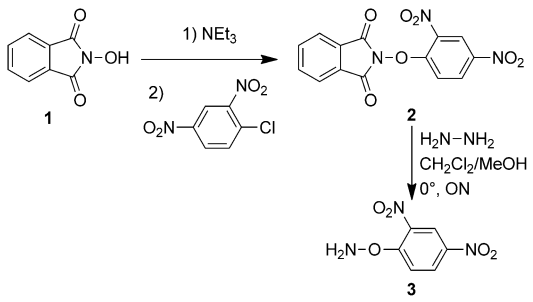
used a modified PHOX ligand,[19] to suit the *N*-benzoylpyridinium ylides substrates.[20] A method of hydrogenation of pyridines through a metal-free pathway was devised with excellent *ee* by Rueping and Antonchick.[21] Herein, we further explored the hydrogenation of *N*-protected pyridines by using N,P-ligated iridium catalysts through the optimization of the reaction.

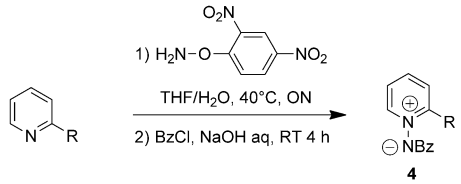
Results and Discussion

The method used to synthesize product **4**, involved only a single step from the commercially available pyridines to be converted into the substrates, once the aminating agent **3** is obtained.[20] The procedure is straightforward, as can be seen in Scheme 1. Compound **1** was deprotonated and coupled by S_EAr to 2,4-dinitrochlorobenzene to afford compound **2** quantitatively. Secondly, the phthalimide group was removed by using a solution of hydrazine in dichloromethane and methanol; this step was also quantitative (see Scheme 1). Finally, 1.2 equivalents of compound **3** were treated with the 2-substituted pyridines, thus generating compounds **4** in up to 68% yield (see Table 1).



Scheme 1. Synthesis of the aminating agent *O*-(2,4 dinitrophenyl)hydroxylamine. ON = overnight.

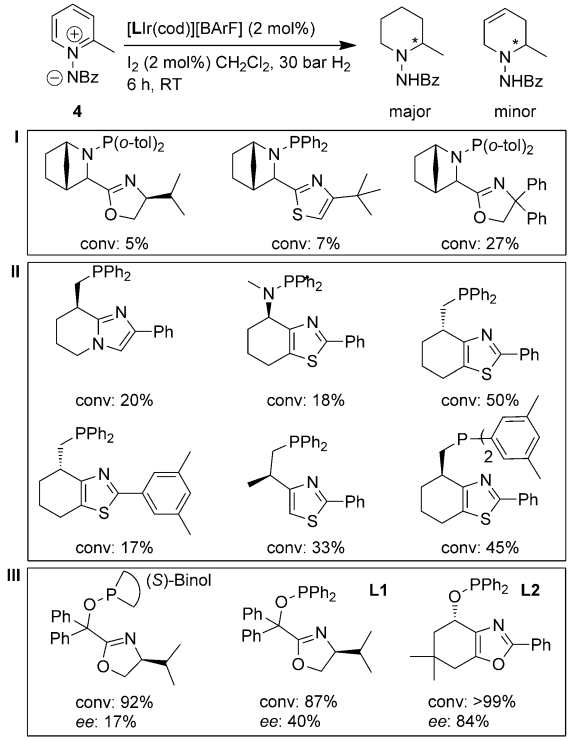
Table 1. Yields of synthesis of the substrate.



Entry	R	Yield [%]	Product
1	Me	67	**4a**
2	Et	55	**4b**
3	*n*Bu	65	**4c**
4	*n*Pent	54	**4d**
5	*i*Pr	43	**4e**
6	Ph	63	**4f**
7	Bn	68	**4g**
8	$(CH_2)_3OBn$	66	**4h**

Bn = benzyl; Bz = benzoyl.

To find the best catalyst, the simplest substrate (compound **4a**), was screened against a library of N,P-ligated iridium catalysts under 30 bars of hydrogen gas pressure, with a 2% catalyst loading and iodine (2%) as an additive (see Scheme 2). Trends can be observed in the behavior of the catalyst based on the electronic and steric characteristics of the ligand. The first class of catalysts to be evaluated, bicyclic catalysts in group **I**, performed very poorly. The low conversions of 5–27% are likely to be a result of their steric bulk. Secondly, the thiazole and imidazole ligated catalysts in group **II** performed somewhat better (18–50% conversion). Finally, the use of ligands containing the oxazole and oxazoline heterocycles gave good to excellent conversion (87- > 99%).



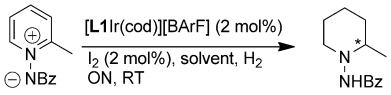
Scheme 2. Screened ligands for asymmetric hydrogenation.

One explanation of these trends is likely to reside in the electronics of the iridium atom. It is logical that the electron-donating ability of the ligand is linked to their basicity, and in turn, affects the electron density at the metal center of the catalyst. Hence, the acidity of the transition metal hydride and the electrophilicity of the iridium atom can be seen as dictated by the ligand effect. This was investigated by Burgess and co-workers.[22] A specific finding from the afore-mentioned study is that the oxygen atom linker adjacent to the phosphorus atom yields a more acidic iridium complex than a similar complex with a carbon atom linker. (pK_a 9.8 vs. 11.5). The iridium center is more electrophilic than rhodium, in part because of its higher oxidation state (Ir^{5+} reactive intermediate), which leads to a higher affinity

for π-electrons, and this characteristic can be amplified by the use of less electron-donating ligands. The electron-rich pyridine ring will bind better to a more electron-poor iridium center. This is supported by the fact that the use of ligand **L2** provides the highest conversion while being the least electron donating; the oxazole is a weaker base than the imidazole or thiazole, and the phosphorous electron density tied to the oxygen atom linker is less available for bonding with the metal center. Subsequently, the *ee* was determined for the reactions with all the ligands of group **III** and found to be highest for ligands **L1** (40%) and **L2** (84%).

As a next step, the effect of solvents as well as the effect of pressure on the reaction was probed to determine the best conditions for the hydrogenation. As can be seen in Table 2, an increase in pressure yielded a slight improvement in *ee* and conversion, whereas a decrease led to a sharp drop in both. Secondly, the use of THF or toluene did not impact the conversion, but did cause a drop in *ee*. The 2,2,3-trimethylpentane was a very poor solvent because of substrate solubility issues.

Table 2. Optimisation of reaction conditions for the hydrogenation.



4 major

Entry	Solvent	Pressure [bar]	Conversion [%][a]	*ee* [%][b]
1	CH_2Cl_2	10	20	–
2	CH_2Cl_2	30	>99	40
3	CH_2Cl_2	50	>99	42
4	toluene	50	>99	25
5	THF	50	>99	30
6	2,2,3-trimethylpentane	50	–	–

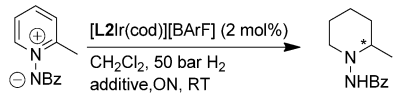
[a] Conversion to the desired product, as measured by NMR spectroscopy. [b] Measured by HPLC on a chiral stationary phase.

As studied by Wang et al.,[15] halogens used as additives often exert a beneficial effect on iridium catalyzed hydrogenation of pyridine-like substrates, thus a small selection was investigated (Table 3). Iodine is commonly used in conjunction with P,P ligands, especially for quinolines and other nitrogen containing heterocycles, in which the iodine acts as a bridging group between two iridium centers, as has been shown by Ng Cheong Chan and Osborn by isolating a P,P ligand complex.[23] In addition, the use of iodine in conjunction with N,P ligands has also been reported by Legault and Charette.[18] The reaction would not proceed without an additive and the use of iodine furnished the highest *ee* of the products. In some cases during screening, a small amount of partly hydrogenated product was obtained.

In all cases, full conversion was achieved. As can be seen from Table 4, the enantioselectivity was strongly affected by the nature of the substituent. Linear alkyl groups provided very similar results (Table 4, entries 1–5) as to be expected, though with a small decrease in *ee* as the chain extended. An increase in bulk immediately adjacent to the pyridine caused a significant drop in selectivity as the bulkier substituents made poor fits for the reaction pocket (Table 4, entries 6 and 7). The reaction with compound **4h** gave the highest *ee*. One might attribute this to a chelation effect of the oxygen atom.[24] As the products were mostly crystalline white solids, a simple recrystallization from boiling ethyl acetate was attempted to improve the *ee* and resulted in an increase of the enantiomeric excess from 90 to 98% in Table 4, entry 8.

In comparison, the results obtained by Legault and Charette were significantly similar. The *ee* obtained for linear alklyl substituents ranged from 78–90%, with a slight decrease in selectivity associated with an increase in chain length. The bulkier benzyl-containing group was hydrogenated with similar results, though both entries 7 and 8 in Table 4 corresponded to a higher *ee* by 2–3%. The hydrogenation of the bulkier groups (*i*Pr and Ph) was not reported by Legault and Charette.[18] Overall, the results are comparable between the two catalysts, with the recrystallization providing an increase in *ee* in all attempted cases (up to 98% in this study, and up to 97% in the earlier study).

Table 3. Screening of the nature and amount of additive.

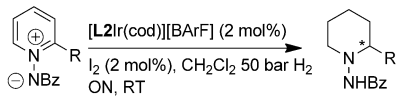


4 major

Entry	Additive	Loading [%]	Conversion [%][a]	*ee* [%][b]
1	I_2	10	20	-
2	I_2	30	>99	40
3	I_2	50	>99	42
4	I_2	50	>99	25
5	Br_2	50	>99	30
6	ICl	50	–	–

[a] Conversion to the desired product, as measured by NMR spectroscopy. [b] Measured by HPLC on a chiral stationary phase.

Table 4. Hydrogenation of substrates.



4 5

Entry	R	Conversion [%][a]	*ee* [%][b]	Product
1	Me	>99	86	**5a**
2	Et	>99	83	**5b**
3	nBu	>99	77	**5c**
4	*n*Pent	>99	77	**5d**
5	*i*Pr	>99	10	**5e**
6	Ph	>99	40	**5f**
7	Bn	>99	61	**5g**
8	$(CH_2)_3OBn$	>99	98[c] (90)	**5h**

[a] Conversion to the desired product, as measured by NMR spectroscopy. [b] Measured by HPLC on a chiral stationary phase. [c] After recrystallization from boiling ethyl acetate.

Conclusions

In conclusion, a series of 2-substituted pyridines were protected and hydrogenated. Following a screening of an N,P-ligated iridium catalysts and halogen additives, the optimal catalyst along with an iodine additive was used to asymmetrically hydrogenate a selection of *N*-iminiumpyridine ylides yielding up to 98% *ee* with a single recrystallization.

Experimental Section

*Synthesis of 2-(2,4-Dinitrophenoxy)-1 H-isoindole-1,3(2 H)-dione (**2**).*[20]

Triethylamine (8.6 mL, 61.6 mmol, 1.1 eq.) was added dropwise to a solution of *N*-hydroxyphthalimide (10.0 g, 61.2 mmol, 1 eq.) in acetone (200 mL) at RT, and the reaction mixture turned dark red. After stirring for 10 min, 2,4-dinitrochlorobenzene (12.4 g, 61.2 mmol, 1 eq.) was added in one portion and after stirring for 2.5 h, the reaction mixture was poured into ice/water slurry (200 mL). The resulting precipitate was filtered and washed with cold MeOH (3×40 mL) followed by cold pentane (3×40 mL) and dried under vacuum to furnish the off-white solid compound **2** in 97% yield (18.6 g) which was used further without any purification. The spectral data of compound **2** matched those reported in literature.[20]

*Synthesis of O-(2,4-Dinitrophenyl)hydroxylamine (**3**).*

A solution of hydrazine hydrate (1.9 mL, 34.2 mmol, 3 eq.) in a MeOH (10 mL) at 0 °C was added dropwise to a solution of compound **2** (3.8 g, 11.4 mmol, 1 eq.) in CH_2Cl_2 (75 mL) at 0 °C. The reaction mixture rapidly became bright yellow and a white precipitate was formed. The suspension was allowed to stand at 0 °C overnight. Cold aq. HCl (55 mL, 1 M) was added and the reaction was shaken vigorously at 0 °C and filtered through a loose cotton plug on a Büchner funnel. The precipitate was washed with MeCN (3×15 mL). The filtrate was poured into separating funnel and the organic phase was separated. The aqueous phase was extracted three times with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the compound **3** in 95% yield (2.15 g), which was used further for the synthesis of substituted compound **4**.[20] The spectral data of compound **3** matched those reported in literature.[20]

*Synthesis of N-Benzoyl(2-butylpyridinium-1-yl)amide (**4c**):*

A mixture of 2-butylpyridine (212 mg, 1.57 mmol, 1.0 equiv.) and 2,4-dinitrohydroxylamine (344 mg, 1.73 mmol, 1.1 equiv.) in THF and H_2O (1:1, 1.2 mL) was heated in a sealed microwave vial at 40 °C for 16 h. The reaction mixture was poured into NaOH (7.0 mL, 2.5 M) at 0 °C and stirred for 20 min., finally freshly distilled BzCl (0.3 mL, 2.36 mmol) was added dropwise while the temperature was maintained at 0 °C. The mixture was stirred at RT for 6 h, before being diluted with H_2O (6.0 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with NaOH (6.0 mL, 2.5 M), dried over $MgSO_4$, evaporated to dryness in vacuo, and the crude yellow compound was purified by silica gel column chromatography with a gradient of 0–4% MeOH in CH_2Cl_2 to afford compound **4d** as an off-white solid in 65% yield (260 mg); m.p. 161.5 °C; R_f=0.48 (10% MeOH in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): δ=0.94 (t, J=7.2 Hz, 3H), 1.42 (sextet, J=7.6 Hz, 2H), 1.74 (quintet, J=8.0 Hz, 2H), 3.11 (t, J=7.6 Hz, 2H), 7.39–7.45 (m, 3H), 7.52 (t, J=7.6 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.88 (t, J=7.6 Hz, 1H), 8.18–8.20 (m, 2H), 8.64 ppm (d, J=6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8, 22.5, 29.2, 31.8, 123.3, 126.5, 128.0, 128.1, 130.1, 137.3, 137.5, 145.8, 157.2, 170.1 ppm; IR (neat): $\tilde{\nu}_{max}$=2957, 1594, 1555, 1490, 1447, 1329, 1293, 1172, 780, 710 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{16}H_{18}N_2O$: 254.3330 $[M]^+$; found: 254.1421, 255.1523, 256.1545.

*Synthesis of N-(2-Pentylpiperidin-1-yl)benzamide (**5d**).*

Catalyst [**L1**Ir(cod)]BArF (2 mg, 1.2 μmol, 2 eq.) was added to compound **4d** (16.5 mg, 0.06 mmol, 1 eq.) in a vial with a stirrer bar, followed by a solution of I_2 in CH_2Cl_2 (0.5 mL, 0.32 mg I_2, 1.2 μmol, 2 eq.). The vial was placed in a high pressure hydrogenation apparatus and the system was purged three times with hydrogen, then filled to 50 bar H_2. The reaction was stirred at room temperature overnight, before the pressure was released and the solvent removed in vacuo. The full conversion was determined by ^{1}H NMR spectroscopy. The crude product was filtered through a short plug of silica gel and the *ee* (77%) was determined by using a HPLC (CHIRALCEL AS-H 250×4,6 mm column, 80% hexane/20% isopropanol, 1 mL min^{-1}). White solid; $[\alpha]_D$=−13.0 (c 0.022, $CHCl_3$); m.p. 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (t, J=6.8 Hz, 3H), 1.24–1.33 (m, 6H), 1.36–1.58 (m, 6H), 1.69–1.87 (m, 5H), 3.30 (brs, -NH, 1H), 7.26 (s, 2H), 7.44 (t, J=7.6 Hz 1H), 7.49–7.53 (m, 1H), 7.75 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1, 22.7, 24.1, 25.3, 25.3, 30.4, 32.3, 33.2, 57.8, 65.2, 127.1, 128.8, 131.6, 166.1 ppm; IR (neat): $\tilde{\nu}_{max}$=2930, 2219, 1593, 1551, 1490, 1329, 2193, 1176, 908, 709 cm^{-1}; HRMS (ESI): m/z: calcd. for $C_{17}H_{26}N_2O$: 274.2045 $[M]^+$; found: 274.2024, 275.2126, 276.2130.

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