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Iridium catalyzed asymmetric hydrogenation of substituted pyridines

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Abstract: We demonstrate here the asymmetric hydrogenation of *ortho*-substituted pyridines using an N,P-ligated iridium catalyst. To facilitate this reaction, aromaticity of the pyridines was weakened by forming *N*-iminopyridium ylides. The reactions gave very high conversions, and after a single recrystallization, excellent *ee* was obtained (up to 98%). This methodology lends itself to the synthesis of chiral piperidine building blocks.

Keywords: Hydrogenation • selective catalysis • homogeneous catalysis • Iridium • Heterocycle

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 synthesise 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, owing to its high efficiency.[4] More recently, homogeneous iridium catalysed asymmetric hydrogenation allows, through excellent enantio-selectivity and atom economy, the efficient synthesis of chiral compounds, especially building blocks.[5]

After Pfaltz' improvement on 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 mono-dentate ligands by the chiral bi-dentate PHOX-ligand (phosphine-oxazoline). These catalysts were able to reduce many olefins, in excellent enantio-selectivities and conversion, that 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 also functionalized olefins.[8] The use of iridium catalysts offers a great advantage over rhodium and ruthenium: the coordination of the olefin takes place through a mono-dentate binding of the substrate via 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 it binds in a bi-dentate 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 aza-cycles employing N,P-ligated iridium catalysts with excellent selectivity (up to >99% *ee*). 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*) using a palladium complex.[12] The use of rhodium and ruthenium to hydrogenate carboxylated aza-cycloalkene has been reported to generate both piperidines and piperazines in very high selectivity.[13] However these methods to synthesize unsaturated aza-cycles require lengthy multi step 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 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 using iridium-Synphos as catalyst.[17] The most successful and very common use of N,P-ligated iridium for the asymmetric hydrogenation of pyridine was conducted by Legault *et al.*[18] using a modified PHOX ligand,[19] in order to suit the *N*-benzoylpyridinium ylides substrates.[20] Here we further explored the hydrogenation of *N*-protected pyridines using N,P-ligated iridium catalysts through

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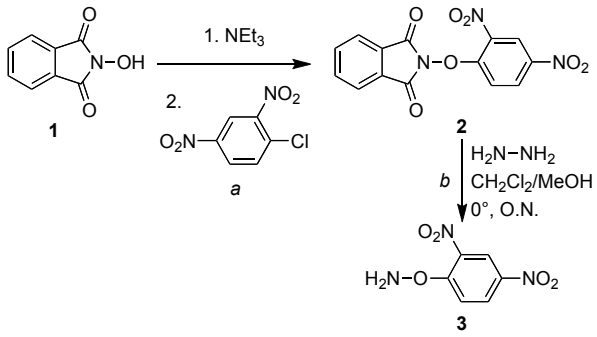
Supporting information for this article is available on the WWW under

the optimization of the reaction.

Results and Discussion



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

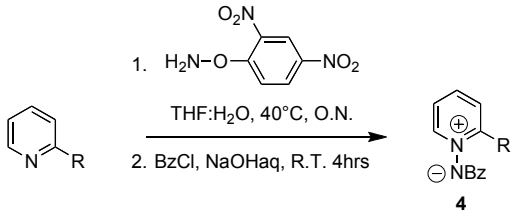


Table 1. Yields of synthesis of the substrate

Entry	*R*	*Yield (%)*	*Product*
1	Me	67	***4a***
2	Et	55	***4b***
3	n-Bu	65	***4c***
4	n-Pentyl	54	***4d***
5	i-Pr	43	***4e***
6	Ph	63	***4f***
7	Bn	68	***4g***
8	(CH2)3OBn	66	***4h***

The method employed to synthesise product **4,** converted the commercially available pyridines in a single step the into the substrates.[20] The procedure is straightforward, as can be seen in Scheme 1. Compound **1** was deprotonated and coupled by S_EAr to Zincke's salt (2,4 *di*nitro-chloro-benzene) to afford compound **2** quantitatively. Secondly, the phthalimide group was removed by a solution of hydrazine in dichloromethane and methanol, this step was also quantitative (see Scheme 1). Finally, 1.2 equivalents of compound **3** were reacted with the 2-substituted pyridines, thus generating compounds **4** in up to 68% yield (see Table 1).

In order to find the best catalyst, the simplest substrate (compound **4a**), was screened against a library of N,P-ligated iridium catalysts using 30 bars of hydrogen gas, 2% catalyst loading and 2% iodine as 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 (5-27%) are to be a result of their steric bulk. Secondly, the thiazole and imidazole (group **II**) ligated catalyst performed somewhat better (18-50%). Finally, the oxazole and oxazoline heterocycles gave good to excellent conversion (87->99%). One explanation of these overall trends in the electronics of the metal center, as affected by the electron donating ability of the ligand, could be the effect of basicity of the ligands on the catalyst and its effect on the acidity of the catalyst's protons, as was investigated by Burgess and co-workers.[21]. Subsequently the *ee* was determined for all the ligands of group **III** and found to be highest for ligands **L1** (40%) and **L2** (84%).

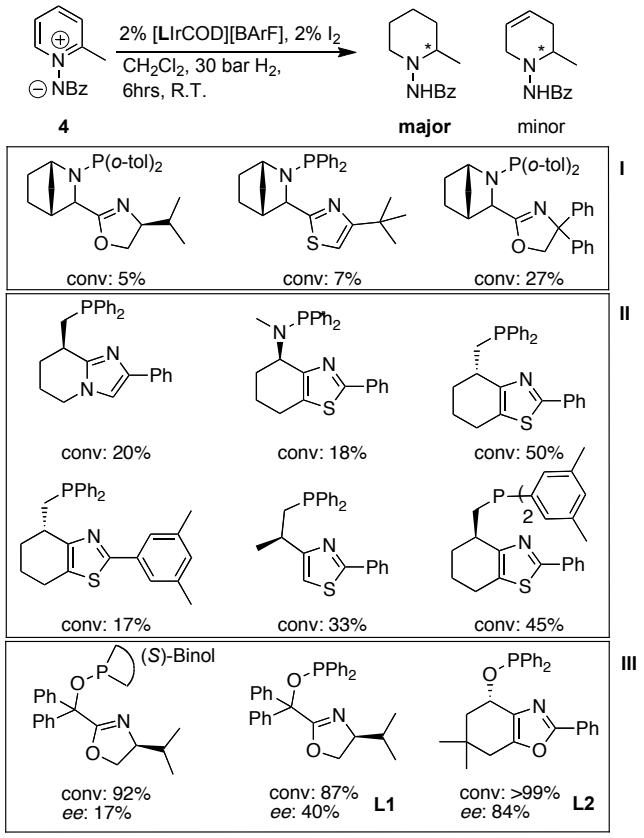


Figure 1. Screened ligands for asymmetric hydrogenation

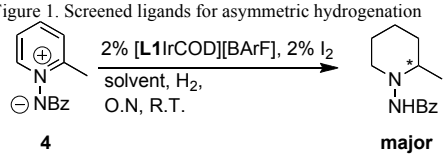


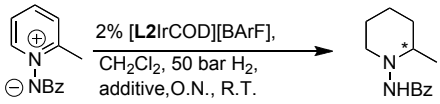
Table 2. Optimisation of reaction conditions for the hydrogenation

Entry	*Solvent*	*Pressure (bars)*	*Conversion (%)*[a]	*ee* (%)[b]
1	*CH_2Cl_2*	*10*	*20*	-
2	*CH_2Cl_2*	*30*	*Full*	*40*
3	*CH_2Cl_2*	*50*	*Full*	*42*
4	*Toluene*	*50*	*Full*	*25*
5	*THF*	*50*	*Full*	*30*
6	*2,2,3 trimethyl-pentane*	*50*	-	-

[a] Measured by NMR spectroscopy. [b] Measured by HPLC, using chiral stationary phase.

As the next step, the effect of solvents as well as the effect of pressure on the reaction was probed, in order to determine the best conditions for the hydrogenation. As can be seen in Table 2, the increase in pressure yielded a slight improvement in *ee* and conversion, whereas a decrease lead 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 due to substrate solubilization issues.

As studied by Wang *et al*,[15] halogens used as additives often exerts a beneficial effect on iridium catalysed hydrogenation of pyridine-like substrates, thus a small selection was investigated. 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 Osborn by isolating a P,P ligand complex.[22] In addition, its use in conjunction with N,P ligands has also been reported.[18,] It was found that the reaction would not proceed without an additive and that iodine furnished the highest *ee* of the products. In some cases during screening, a small amount of partly hydrogenated product was observed.



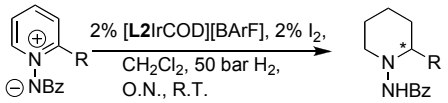
4 **major**

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

Entry	*Additive*	*Loading (%)*	*Conversion (%)[a]*	*ee (%)[b]*
1	I_2	*0*	-	-
2	I_2	*1*	*Full*	*64*
3	I_2	*2*	*Full*	*86*
4	I_2	*4*	*Full*	*35*
5	Br_2	*2*	*Full*	*63*
6	*ICl*	*2*	*full*	*50*

[a] Measured by NMR spectroscopy. [b] Measured by HPLC, using chiral stationary phase.

In all cases, full conversion was observed. As can be seen from Table 4, the enantioselectivity was strongly affected by the nature of the substituent. Linear alkyls provided very similar results (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 (entries **6-7**). Compound **9**, gave the highest *ee*. One might attribute this to chelation effect of the oxygen atom.[24] As the products were mostly crystalline white solids, a simple recrystallisation from boiling ethyl acetate was attempted to improve the *ee* and resulted in an increase of the enantiomeric excess from 90 to 98% in entry **9**.



4 **5**

Table 4. Hydrogenation of substrates.

Entry	*R*	*Conversion (%)[a]*	*ee (%)[b]*	*Product*
1	Me	Full	86	***5a***
2	Et	Full	83	***5b***
3	*n*-Bu	Full	77	***5c***
4	*n*-Pentyl	Full	77	***5d***
5	*i*-Pr	Full	10	***5e***
6	Ph	Full	40	***5f***
7	Bn	Full	61	***5g***
8	(CH2)3OBn	Full	*98[c] (90)*	***5h***

[a] Measured by NMR spectroscopy. [b] Measured by HPLC, using chiral stationary phase. [c] After recrystallization from boiling ethyl acetate.

Conclusion

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(2H)-dione (2).[20]

To a solution of solution of N-hydroxyphthalimide (10.0 g, 61.2 mmol, 1 eq) in acetone (200 mL), triethylamine (8.6 mL, 61.6 mmol, 1.1 eq) was added dropwise at R.T. and reaction mixture turned dark red. After stirring for 10 min, 2,4-dinitro chlorobenzene (12.4 g, 61.2 mmol, 1 eq) was added in one portion and after stirring for 2.5 hrs, the reaction mixture was poured into 200 mL of ice/water slurry. The resulting precipitate was filtered and washed with cold MeOH (3 x 40 mL) followed by cold pentane (3 x 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 ^oC. The reaction mixture rapidly became bright yellow and a white precipitate was formed. The suspension was allowed to stand at 0 ^oC overnight. Cold 1 M HCl_{aq} (55 mL) was added and reaction was shaken vigourously at 0 ^oC and filtered through a loose cotton plug on a Büchner funnel. The precipitate was washed with MeCN (3 x 15 mL). The filtrate was poured into separatory funnel and the organic phase was separated. The aqueous phase was extracted three times with CH_2Cl_2 (3 x 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 eq.) and 2,4-dinitrohydroxylamine (344 mg, 1.73 mmol, 1.1 eq.) in THF and H_2O (1:1, 1.2 mL) was heated in a sealed microwave vial at 40 ^oC for 16 hrs. The reaction mixture was poured into into 2.5 M NaOH (7.0 mL) at 0 ^oC 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 R.T. for 6 hrs, before being diluted with H_2O (6.0 mL) and extracted with CH_2Cl_2 (3 x 50 mL) and the organic layer was washed with 2.5 M NaOH (6.0 mL), dried over $MgSO_4$, evaporated to dryness *in vacuo* and the crude yellow compound was purified by silica gel column chromatography using a gradient of 0-4% MeOH in CH_2Cl_2 to afford compound **4d** as an off-white solid in 65% (260 mg), mp = 161.5 °C; R_f = 0.48 (10 % MeOH in CH_2Cl_2).^{1}HNMR (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 (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; IR (neat, cm^{-1}): ν_{max} = 2957, 1594, 1555, 1490, 1447, 1329, 1293, 1172, 780, 710; HRMS(ESI): m/z = 254.1421, 255.1523 (M^++1), 256.1545 (M^++2).mol. formula: $C_{16}H_{18}N_2O$; mol. wt: 254.33.

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

Catalyst [**L1**IrCOD]BArF (2mg, 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 g I_2, 1.2 µmol, 2% eq). The vial was placed in ahigh pressure hydrogenation apparatus and the system was purged three times with hydrogen, then filled to 50 bars 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 x 4,6 mm column, 80% hexane-20% *iso*propanol, 1mL/min). White solid; $[\alpha]_D$ = -13.0 (c 0.022, $CHCl_3$);mp = 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 (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; IR (neat, cm^{-1}): ν_{max} = 2930, 2219, 1593, 1551, 1490, 1329, 2193, 1176, 908,709 HRMS(ESI): m/z = 274.2024, 275.2126 (M^++1), 276.2130 (M^++2); mol. wt: 274.40; mol. formula: $C_{17}H_{26}N_2O$.

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