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Enantioselective Hydrogenation of Imidazo[1,2-*a*]pyridines

Christoph Schlepphorst, Mario P. Wiesenfeldt and Frank Glorius*

Abstract: The enantioselective synthesis of tetrahydroimidazo[1,2-*a*]pyridines via direct hydrogenation was achieved using a ruthenium/N-heterocyclic carbene (NHC) catalyst. The reaction forgoes the need for protecting or activating groups, proceeds with complete regioselectivity, good to excellent yields, enantiomeric ratios of up to 98:2, and tolerates a broad range of functional groups. 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridines, which are found in numerous bioactive molecules, are directly obtained by this method and its applicability was demonstrated by the (formal) synthesis of several functional molecules.

Chiral saturated heterocycles are prevalent in secondary metabolites and, as a result, have been exploited as biologically active building blocks as well as synthetic intermediates especially in pharmaceutical and agrochemical research.[1] Traditionally, these motifs are prepared via enantioselective cycloadditions or cyclizations which often require tedious multistep substrate syntheses and provide a limited scope.[2] Alternatively, the enantioselective hydrogenation of readily available heteroarenes has recently emerged as a straightforward route to access these valuable motifs.[3] However, some common obstacles have to be addressed. These include the aromatic stabilization and the ability of some substrates as well as their corresponding products, especially those containing nitrogen, to bind to the catalyst. This can lead to catalyst deactivation as well as diminished enantioselectivity due to the undesired binding competition with the productive coordination of the unsaturated ring system. Consequently, methods to lower the inherent aromaticity of heterocycles and/or prevent binding to the metal catalyst have been employed for the reduction of N-heterocycles.[4] Likewise, examples for the direct hydrogenation of N-,[3,5] O-,[6] S-,[4b,7] and all-carbocyclic aromatic compounds[8] are known.

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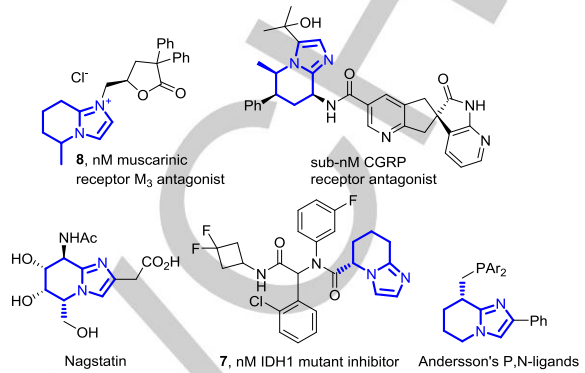

Figure 1. Bioactive molecules and chiral ligands containing the substituted tetrahydroimidazo[1,2-*a*]pyridine scaffold.

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyridines are found in numerous bioactive molecules including those outlined in Figure 1.[9] Furthermore, Andersson and co-workers developed a series of chiral P,N-ligands based on this framework, which show distinct reactivity and high enantioinduction in Ir-catalyzed hydrogenations and Pd-catalyzed intermolecular Heck reactions.[10] However, to the best of our knowledge, no catalytic enantioselective method to construct the chiral substituted 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine core has been reported to date, and either enantio-enriched starting materials or chiral resolution techniques have to be employed to access the desired enantiopure products. Based on our previous studies in the field of enantioselective arene hydrogenation,[5g,6a,b,7,8a,11] especially a study concerning the enantioselective reduction of indolizines,[11] we envisaged that our ruthenium–N-heterocyclic carbene (NHC[12]) catalyst could be effective in the catalytic reduction of imidazo[1,2-*a*]pyridines. Herein, we disclose a direct ruthenium–NHC-catalyzed enantioselective hydrogenation of imidazo[1,2-*a*]pyridines to afford chiral 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines.

In an initial experiment, readily accessible 5-methylimidazo[1,2-*a*]pyridine **1a** was reacted with the *in situ* prepared $Ru(NHC)_2$ catalyst[13] in *n*-hexane under 70 bar hydrogen pressure at 25 °C (Table 1). The reaction cleanly generated the desired tetrahydroimidazo[1,2-*a*]pyridine **2a** with 50% conversion and an enantiomeric ratio of 90:10. No side products were detected. The observed chemoselectivity was in line with the results obtained for the indolizine hydrogenation and can be explained by the preservation of one aromatic imidazole ring in the product. Due to the bridge head nitrogen, a neutral aromatic resonance structure after partial reduction can only be drawn in the five-membered ring, which is in sharp contrast to other bicyclic heteroarenes, such as azaindoles.[5h] Note that Zhou's enantioselective hydrogenation of activated pyrrolo[1,2-*a*]pyrazinium salts[4c] likewise results in the reduction of the six-membered ring. Exploration of the reaction conditions revealed that *tert*-amyl alcohol was the best solvent in terms of both yield and e.r. (entries

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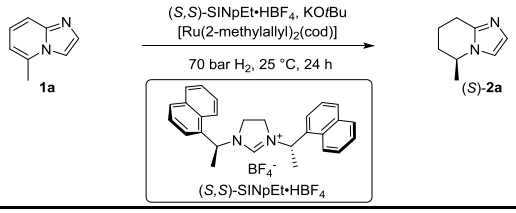
1–6). Full conversion was achieved by a simple increase of the hydrogen pressure from 70 to 100 bar and thus enabled the isolation of **2a** in quantitative yield after a facile acid/base extraction (entry 7). A decrease of the reaction temperature from 25 °C to 0 °C led to an increase of the e.r., however, the conversion was slightly reduced (entry 8). X-ray crystallographic analysis of the corresponding hydrochloride salt confirmed the structure and revealed its absolute configuration.

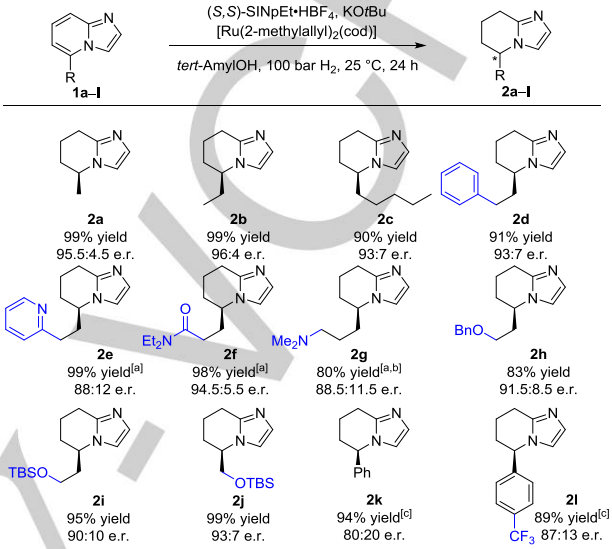
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Conversion[b]	E.r.[c]
1	*n*-hexane	50%	90:10
2	Et_2O	68%	94.5:5.5
3	toluene	64%	71:29
4	THF	59%	94:6
5	$PhCF_3$	87%	85:15
6	*t*-AmylOH	93%	95.5:4.5
7[d]	***t*-AmylOH**	**99% (99%)**[e]	**95.5:4.5**
8[d,f]	*t*-AmylOH	74%	98:2

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.02 mmol), KOt-Bu (0.04 mmol) and (*S,S*)-SINpEt·HBF$_4$ (0.04 mmol), **1a** (0.2 mmol), solvent (1 mL). See the Supporting Information for detailed experimental conditions. [b] The conversion was determined by ^{1}H-NMR. [c] The e.r. was determined by chiral HPLC. [d] The reaction was performed under 100 bar H_2 pressure. [e] Isolated yield in parentheses. [f] The reaction was performed at 0 °C. *tert*-AmylOH = 2-methyl-2-butanol. Cod = 1,5-Cyclooctadiene.

Under the optimized reaction conditions, a series of 5-substituted imidazo[1,2-*a*]pyridines were hydrogenated to the corresponding 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines **2** in high yields and enantioselectivities (Schemes 1 and 2).[14] Many functional groups such as pyridines, amides, amines, (silyl)-ethers, esters and different halides were well-tolerated offering opportunities for further functionalization of the obtained products. An increase in chain length of the 5-substituent (substrates **2b–d**, Scheme 1) hardly affected the enantioselectivity, while excellent yields were maintained. The comparison of the results for the structurally similar phenethyl- and pyridinylethyl products (**2d** and **2e**) indicated that an additional Lewis-basic coordination ability could lead to a slight decrease in enantiocontrol. A similar observation was made for the amide and amine substrates **1f** and **1g**. Substrates **1e–g** were converted into their corresponding products in excellent yields after a slight increase of concentration and hydrogen pressure. Benzyl- and silyl protected alcohols **1h–j** were also successfully hydrogenated.[15] Note that no debenzylation was observed in the hydrogenation of **1h** illustrating the mild reaction conditions and orthogonality to Pd-catalyzed hydrogenolysis. The products **2i** and **2j** were purified by chromatography due to their rapid desilylation upon exposure to acid. Substrates **1k** and **1l** bearing sterically and electronically distinct aryl groups were also converted to the corresponding products in excellent yields, albeit with diminished e.r.



Scheme 1. Substrate scope of 5-substituted imidazo[1,2-*a*]pyridines **1a–l**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.02 mmol), KOt-Bu (0.04 mmol) and (*S,S*)-SINpEt·HBF$_4$ (0.04 mmol), **1a–l** (0.2 mmol), *t*-AmylOH (1 mL). Yields of isolated products are given. Absolute configurations are assigned in analogy to **2a**. [a] The reaction was performed at 0.3 M concentration and 150 bar H_2 pressure. [b] Isolated product contains 4% of inseparable starting material. [c] The reaction was performed in *n*-hexane. TBS = *tert*-butyldimethylsilyl.

Next, the effect of an additional substituent on the imidazole ring on the reaction outcome was investigated (Scheme 2). Hydrogenation of the substrate bearing a phenyl substituent in the 2-position (**1m**) provided the corresponding product with preserved high yield and enantiocontrol. A variety of functional groups were tolerated on the aryl group (**2n–s**) without loss of enantioselectivity. Only a methoxy substituent in *para*-position (**2s**) led to both diminished yield and e.r. A substrate bearing a cyano group (**1r**) could be hydrogenated with high enantioselectivity and complete reduction of the nitrile to a benzylic primary amine. The generally somewhat lower yields of disubstituted products, in the absence of any side products, compared to **2a–l**, were identified to be caused by the lower solubility of the hydrochloride salts in the aqueous phase during the workup procedure. Therefore, **2q** was purified by chromatography instead, giving a substantially increased yield of 92% compared to 31% after extractive workup. Moreover, the hydrogenation of imidazo[1,2-*a*]pyridines with functional groups directly attached to the imidazole ring was possible, as exemplified by products **2t** and **2u**, which could be isolated in good to excellent yields and e.r. values. 2,5-Disubstituted silyl protected alcohol **2v** could also be isolated in quantitative yield and good enantioselectivity showcasing that the methyl group is

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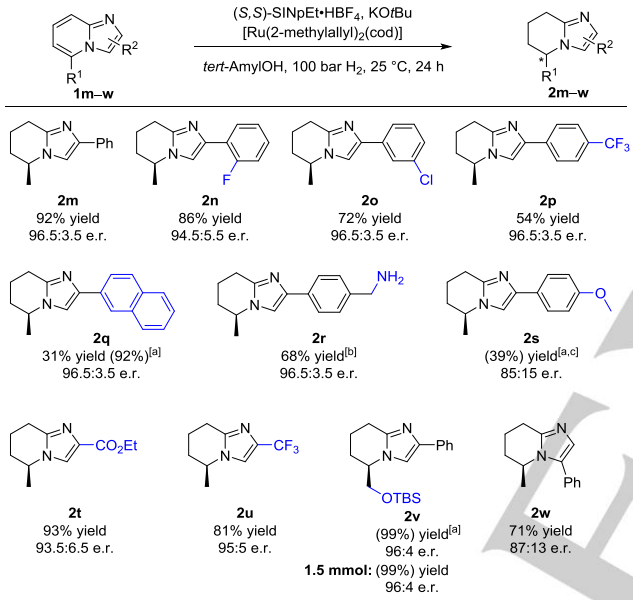
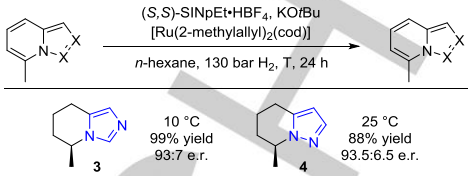
not a necessity for this substitution pattern. Scale-up of the reaction to 1.5 mmol was shown for this substrate. No decrease in yield or enantioselectivity was observed. 5-Methyl-3-phenylimidazo[1,2-*a*]pyridine **1w** bearing the substituents in closer proximity delivered the corresponding product **2w** in conserved high yield, albeit with diminished e.r.

In order to show the applicability of this method towards other structurally related nitrogen-rich heterocycles, an imidazo[1,5-*a*]pyridine derivative as well as a pyrazolo[1,5-*a*]pyridine were efficiently reduced in good yield and e.r.. **3**, whose configuration was proven by x-ray crystallographic analysis, and **4** were obtained from the corresponding starting materials, indicating the generality of the catalyst towards azaindolizine substrates in terms of reactivity as well as chemo- and enantioselectivity (Scheme 3).

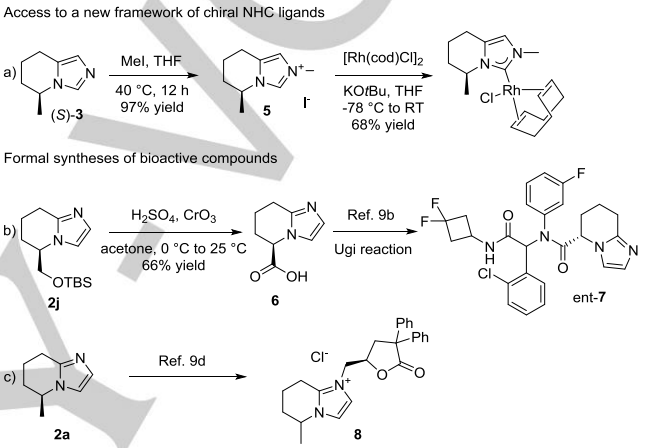


Scheme 2. Substrate scope of disubstituted imidazo[1,2-*a*]pyridines **1m–w**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.02 mmol), KOt-Bu (0.04 mmol) and (*S,S*)-SINpEt·HBF$_4$ (0.04 mmol), **1m–w** (0.2 mmol), *t*-AmylOH (1 mL). Yields of isolated products after acid/base extraction are given. [a] Isolated yield after column chromatography instead is given in parentheses. [b] The corresponding nitrile compound **1r** was used as substrate. [c] The reaction was performed at 0.3 M concentration and 150 bar H_2 pressure.

To demonstrate the synthetic utility of this method, further derivatizations and applications were carried out (Scheme 4). Firstly, we sought to apply our method to the synthesis of new chiral NHC ligands.[16] Methylation of **3** with methyl iodide proceeded smoothly to generate imidazolium salt **5**, which could be further reacted with [Rh(cod)Cl]$_2$ proving its ability to act as a ligand (Scheme 4a). Furthermore, silyl ether **2j** was deprotected and oxidized in the same reaction under Jones-oxidation conditions to provide carboxylic acid **6** in 66% yield. This compound can undergo an Ugi reaction to yield the IDH1 mutant inhibitor **7** as demonstrated by Zhou (Scheme 4b).[9b] Finally, the muscarinic receptor antagonist **8** can be prepared in one step from **2a** as shown by Kaiser (Scheme 4c).[9d] Note that the authors used racemic **2a** in their study, obtained by heterogeneous hydrogenation of **1a**. The targeted synthesis of diastereomers is now feasible using our method.



Scheme 3. Enantioselective hydrogenation of 5-methylimidazo[1,5-*a*]pyridine and 7-methylpyrazolo[1,5-*a*]pyridine. Yields of isolated products are given.



Scheme 4. Synthesis of functional molecules containing the tetrahydro-imidazopyridine scaffold.

In summary, we have developed the first enantioselective catalytic synthesis of 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines, which are found in numerous bioactive molecules, via direct hydrogenation of readily available imidazo[1,2-*a*]pyridines, using a ruthenium–NHC-catalyst. The reported method is completely regioselective, and the corresponding products are obtained in good to excellent yields and enantioselectivities. To showcase the applicability of this newly developed method, two direct precursors for bioactive molecules as well as a novel chiral NHC ligand derived from an imidazo[1,5-*a*]pyridine were synthesized. The application of this protocol as a platform for the preparation of useful three-dimensional functional heterocycles is anticipated.

Experimental Section

General procedure: [Ru(2-methylallyl)$_2$(cod)] (6.3 mg, 20 µmol, 0.1 equiv.), KO*t*Bu (4.5 mg, 40 µmol, 0.2 equiv.) and SINpEt•HBF$_4$ (18.7 mg, 40 µmol, 0.2 equiv.) were stirred at 70 °C in *n*-hexane (1 mL) for 16 h to yield a yellow suspension of the ruthenium bis-NHC complex. The mixture was added to the imidazo[1,2-*a*]pyridine substrate **1** (0.2 mmol, 1 equiv.) in a 7 mL dram vial under an argon atmosphere and the solvent was removed *in vacuo*. *tert*-Amyl alcohol (0.7 mL, 0.3 M or 2 mL, 0.1 M) was added and the vial was transferred to an argon filled 150 mL stainless-steel reactor. The autoclave was purged with hydrogen gas four times before the reaction pressure was set to 100 bar (or 150 bar). The hydrogenation reaction was performed at 25 °C for 24 hours. After the autoclave was carefully depressurized, the mixture was concentrated *in vacuo* and

purified by acid/base extraction or flash chromatography on silica gel to afford the desired product **2**.

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Keywords: enantioselective hydrogenation • N-heterocyclic carbenes • imidazopyridines • ruthenium • heterocycles

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The enantioselective hydrogenation of imidazopyridines was achieved using a ruthenium(II)-NHC catalyst. Excellent yields and enantioselectivities are obtained and a variety of functional groups is tolerated. This method provides straightforward access to valuable enantio-enriched tetrahydroimidazopyridines from readily available aromatic precursors, and its applicability was demonstrated by the synthesis of direct precursors to bioactive molecules and a novel chiral NHC ligand.