Asymmetric Catalysis

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Asymmetric Hydrogenation of Pyridinium Salts with an Iridium Phosphole Catalyst**

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Abstract: *Iridium-catalyzed asymmetric hydrogenation of N-alkyl-2-alkylpyridinium salts provided 2-aryl-substituted piperidines with high levels of enantioselectivity. Simple benzyl and other alkyl groups successfully activated the challenging pyridine substrates toward hydrogenation. The use of the unusual chiral-phosphole-based MP^2-SEGPHOS was the key to the success of this approach which provides a versatile and practical procedure for the synthesis of chiral piperidines.*

Hydrogenation of readily available substituted pyridines is a straightforward and atom-economical approach for the preparation of substituted piperidines.[1] These piperidines are ubiquitous structural motifs in natural products as well as key pharmacophores in many active pharmaceutical ingredients (Figure 1).[2]

Despite the advances made in the asymmetric hydrogenation of other nitrogen-containing heterocycles such as quinolines and isoquinolines,[1c,3] examples of direct asymmetric hydrogenations of pyridines remain scarce. In 2000, Studer and co-workers reported the asymmetric reduction of pyridines in 27% *ee* using rhodium bis(phosphine) complexes.[4] Zhou's [{Ir(cod)Cl}$_2$]/(*S*)-MeO-Biphep system reduced the related 7,8-dihydroquinolin-5(6*H*)-one substrates with good enantioselectivities. However, the system was not general for pyridines.[5]

Recognizing that the major obstacle to achieving highly efficient asymmetric hydrogenations of pyridines is overcoming the thermodynamic stability associated with the aromaticity of the pyridine ring, a number of approaches have been explored to circumvent this issue.[6,7] Charette and co-workers have employed *N*-iminopyridinium ylides to improve the reactivity of the pyridine ring and achieve efficient asymmetric hydrogenation.[8] Most recently, Zhou and co-workers have reported the successful asymmetric hydrogenation of *N*-(2-CO$_2$*i*Pr)benzylpyridinium salts where the ester is believed to act as a directing group for the catalyst [Eq. (1); Boc = *tert*-butoxycarbonyl].[9] Extra steps are required for removing the activating groups to obtain the desired piperidine product. Given that simple *N*-alkylpiperidines themselves are valuable synthons, an asymmetric hydrogenation method which utilizes simple *N*-alkylpyridinium salts would increase the scope and utility of this approach. Herein, we report a highly efficient asymmetric hydrogenation of simple *N*-alkyl-2-arylpyridinium salts with excellent reactivity and enantioselectivity using an iridium phosphole catalyst [Eq. (2)].

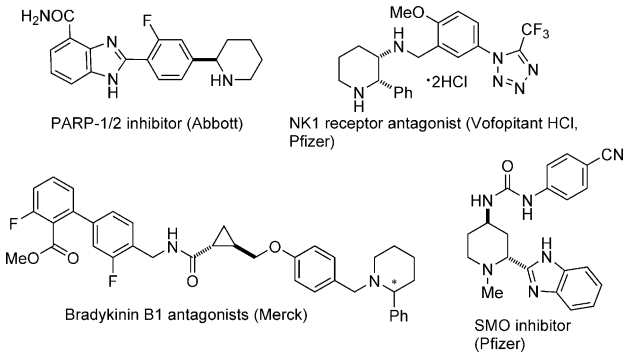
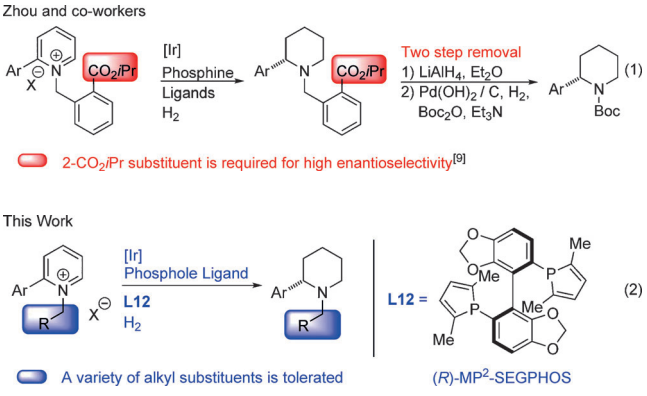


Figure 1. Selected pharmaceutical targets.

For our initial studies, an *N*-benzyl group was chosen to activate 2-phenylpyridine because of its ubiquity in protect-



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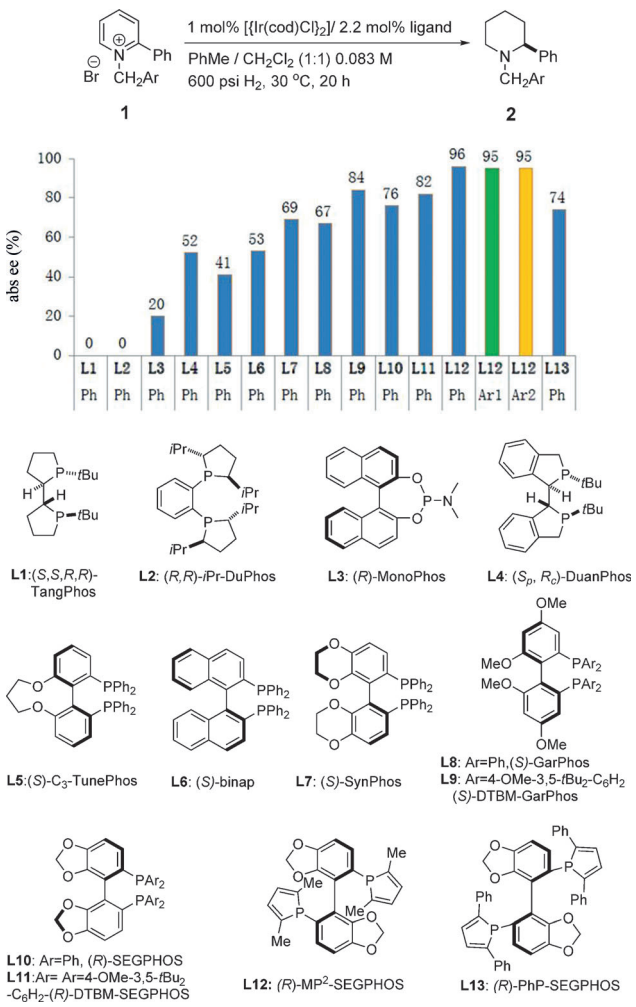
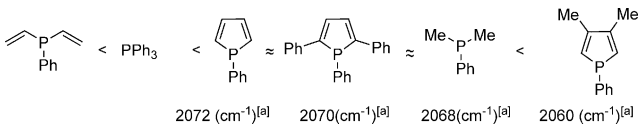


Figure 2. Selected results of ligand screen for asymmetric hydrogenation of *N*-alkyl-2-phenylpyridium bromide substrates using iridium catalysts. Reactions were carried out using 0.01 mmol of substrate in 0.12 mL of mixed solvent. Absolute enantiomeric excesses were determined by SFC using a chiral stationary phase. Ar1 = 2-$MeCO_2C_6H_4$ and Ar2 = 4-$MeOC_6H_4$ for the Ar group in **1**. cod = 1,5-cyclooctadiene.

ing-group chemistry (Figure 2).[10] While simple *N*-benzylpyridinium salts have been demonstrated to be very challenging substrates in asymmetric hydrogenation, we envisioned that an in depth evaluation of ligand architecture with respect to reaction selectivity might result in the identification of an efficient catalyst. A library of 240 chiral phosphine ligands was evaluated. While the majority of phosphine ligands screened gave less than 60% *ee*, several active and selective ligands were discovered. Doubly oxygenated atropisomeric C_2-symmetric bis(phosphine) ligands, such as SynPhos, SEGPHOS, and GarPhos, in conjunction with [{Ir(cod)Cl}$_2$] as a precatalyst showed good enantioselectivities in the asymmetric hydrogenation of **1a** (**L7–L11;** Figure 2). The fine-tuning of the GarPhos and SEGPHOS ligands structure also had notable impact on their enantioselectivities, with more sterically encumbered and electron-rich phosphine aryl substituents giving higher enantioselectivities (**L8**, **L9**, and **L10**, **L11**). In addition, generally higher selectivities were observed with more electron-rich doubly oxygenated ligand frameworks. When the phosphole-containing MP^2-SEGPHOS (**L12**) was employed, the chiral piperidine **2** (Ar = Ph) was obtained in 96% *ee*. High *ee* values were also observed for two other structurally diverse *N*-benzylpyridinium bromides (Ar = 2-$MeCO_2C_6H_4$ and 4-$MeOC_6H_4$), thus suggesting that a general protocol might be achievable. The size of the phosphole substituents was found to be critical (**L12** and **L13**), as evidenced by the increased selectivity when a less sterically encumbered phosphole was employed.

It is worth noting that to the best of our knowledge the results obtained with **L12** represent the first reported examples of the use of MP^2-SEGPHOS in a highly efficient asymmetric reaction.[11] A number of unique features of phospholes may contribute to the observed high efficiency and enantioselectivity in the reactions employing MP^2-SEGPHOS as a ligand. Firstly, the previously noted relationship between the selectivity of the asymmetric hydrogenation and donor capacity of the ligand would be further enhanced by the phosphole functionality of MP^2-SEGPHOS (Scheme 1).[12] Secondly, the rigidity[13] and planarity[14] of the phosphole unit would be expected to provide a well-defined chiral pocket[15] around the reactive site which is substantially different from those seen with other C_2-symmetric bis(phosphine) ligands.

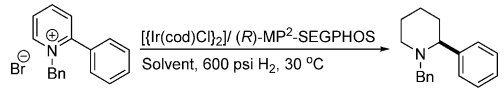


Scheme 1. Order of electron-donating ability of phosphorus ligands. [a] Infrared data for [LMo(CO)$_5$] complexes.[12] Only the highest energy ν(CO) is given.

Having identified MP^2-SEGPHOS as the most selective ligand of those examined, we next explored the influence of solvent (Table 1). While many single solvents led to excellent enantioselectivity for **1a**, acceptable reactivity was only observed for THF, acetone, and 1,2-dichloroethane (DCE) with 2 mol% of the iridium catalyst. The combination of acetone and DCE proved optimal (Table 1, entry 10), thus allowing the iridium catalyst loading to be lowered to 0.5 mol%.

To explore the utility of the newly developed Ir/MP^2-SEGPHOS catalytic system, a range of *N*-benzyl-2-substituted pyridium bromide substrates were synthesized and studied under the optimized reaction conditions. The results are summarized in Table 2. For all chosen 2-arylpyridinium substrates (entries 1–15), the chiral products **2a–m** were obtained in excellent yield and selectivity (90% to 96% *ee*). The catalytic system worked well for *ortho*-substituted, sterically hindered substrates such as **1d**, **1k**, and **1m** (entries 4, 12, and 15), thus highlighting the enhanced reactivity of this system. The enantioselectivities in these cases were only slightly less than those where the 2-aryl group bore substituents in the *meta* or *para* positions. Significantly, the electronic properties of the 2-aryl group did not exert any noticeable effect on the reaction selectivity. Both the elec-

Table 1: Solvent screening for asymmetric hydrogenation of *N*-benzyl-2-phenylpyridium bromide using an Ir/(*R*)-MP^2-SEGPHOS catalyst.[a]

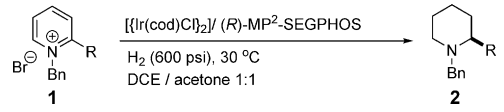


1a **2a**

Entry	Solvent	Conversion [%][b]	*ee* [%][b]
1	CH_2Cl_2	53	93
2	DCE	>99	94
3	EtOAc	57	94
4	acetone	>99	94
5	1,4-dioxane	62	93
6	toluene	22	89
7	THF	>99	89
8	MeOH	32	63
9[c]	acetone	91	86
10[c]	DCE/acetone (1:1)	>99	93
11[c]	DCE	78	95

[a] Reaction conditions: **1a** 0.083 M, [Ir]/ligand/*N*-benzyl-2-phenylpyridium bromide = 2:2.2:100, 20 h. [b] Conversions and enantiomeric excesses were determined by SFC using a chiral stationary phase. [c] **1a** 0.025 M, [Ir]/ligand/*N*-benzyl-2-arylpyridium bromide = 0.5:0.55:100, 20 h.

Table 2: Iridium-catalyzed asymmetric hydrogenation of the *N*-benzyl-2-substituted pyridinium salts **1**.[a]



1 **2**

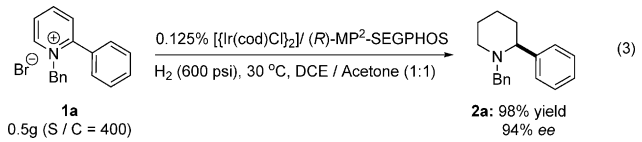
Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	C_6H_5 (**1a**)	**2a**	97	96
2	3-MeC_6H_4 (**1b**)	**2b**	99	96
3	4-MeC_6H_4 (**1c**)	**2c**	93	93
4	2-$MeOC_6H_4$ (**1d**)	**2d**	90	90
5	3-$MeOC_6H_4$ (**1e**)	**2e**	99	96
6	4-$MeOC_6H_4$ (**1f**)	**2f**	95	94
7	4-Ac(H)NC_6H_4 (**1g**)	**2g**	97	95
8	4-*t*BuC_6H_4 (**1h**)	**2h**	96	93
9	4-ClC_6H_4 (**1i**)	**2i**	96	95
10	4-PhC_6H_4 (**1j**)	**2j**	86	90
11[d]	4-PhC_6H_4 (**1j**)	**2j**	96	95
12	2,4-$Cl_2C_6H_3$ (**1k**)	**2k**	94	90
13	3,5-$F_2C_6H_3$ (**1l**)	**2l**	95	96
14	2-naphthyl (**1m**)	**2m**	12	93
15[e]	2-naphthyl (**1m**)	**2m**	88	94
16[e]	Me (**1n**)	**2n**	81	33
17[e]	*i*Pr (**1o**)	**2o**	24	69
18[f]	CH_2OAc (**1p**)	**2p**	92	24
19[f,g]	Bn (**1p**)	**2p**	94	42

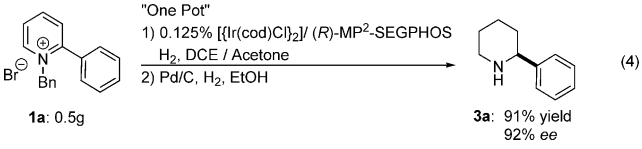
[a] Reaction conditions: **1** 0.025 M, [Ir]/ligand/*N*-benzyl-2-arylpyridium bromide = 0.5:0.55:100, 20 h. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by SFC or HPLC using a chiral stationary phase. [d] DCE/acetone = 5:1 as solvent. [e] Acetone as solvent. [f] DCE as solvent. [g] **L13** was used as ligand.

tron-donating 4-MeO (**1f**) and electron-withdrawing 4-Cl (**1i**), and 3,5-F_2-phenyl-substituted (**1l**) substrates provided similarly high enantioselectivities (entries 6, 9, and 13). During our study, we observed that some substrates were quite sensitive to the solvent composition, thus requiring adjustment of the solvent ratio to achieve higher reactivity (entries 10 and 11, and 14 and 15). For 2-alkylpyridinium substrates, chiral products were obtained with only low to moderate levels of enantioselectivity (entries 16–19). While improved enantioselectivity was observed with a sterically bulky substrate (**1o** versus **1n**), the yield of the isolated product fell significantly because of the lower reactivity (entries 16 and 17). Notably, tuning the phosphole ligand structure had some impact on the levels of enatioselectivity for the 2-benzylpyridinium substrate (**1p**) (entries 18 and 19). When using **L13**, the desired product **2p** was obtained in 42% *ee*.

To evaluate the practical utility of the newly developed method, the asymmetric hydrogenation of *N*-benzyl-2-phenylpyridium bromide (**1a**) was carried out on a .5 mmol scale. The desired product **2a** was obtained in 98% yield and 94% *ee* [Eq. (3)], and the catalyst loading could be reduced to 0.25 mol% (S/C = 400) at this scale. The facile removal of the N-benzyl group was demonstrated through a one-pot asymmetric hydrogenation followed by deprotection, thus giving 2-phenylpiperidine in 91% overall yield and 92% *ee* [Eq. (4)].

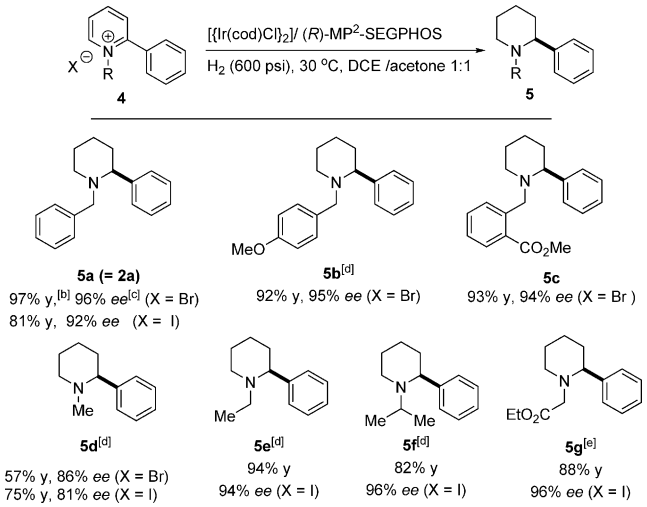
Having established a robust reaction with *N*-benzyl derivatives, we wished to explore the substrate scope with





other *N*-alkyl substituents. As shown in Scheme 2, the iridium phosphole catalyst delivered remarkably high conversion and enantioselectivity with *N*-alkyl substituents as small as Et (**5e**), and even an *N*-methylpyridinium salt gave the resulting *N*-methylpiperidine product in good yield and 81% *ee* (**5d**). The (carboethoxy)methyl substituent (**5g**) was also tolerated, thus giving enantioselectivities comparable to those seen with benzyl substituents (**5a**). This substituent is particularly interesting because of its utility as a functional group for further elaboration. The nature of the pyridinium counterion had some impact on both the activity and enantioselectivity of the reaction (**5a** and **5d**). The counterion effect is not yet understood,[16] and we are currently investigating its origin.

In summary, we have developed a highly efficient enantioselective hydrogenation of *N*-alkyl-2-arylpyridinium salts. This protocol represents a significant advance over previous methods in that a directing group is not required. With this constraint removed, this new method tolerates a variety of *N*-benzyl as well as simple *N*-alkyl groups, which greatly increases the scope and applicability of this approach in synthesis. In addition, this work provides the unique example of using a chiral-phosphole-based ligand for highly



Scheme 2. Iridium-catalyzed asymmetric hydrogenation of the 2-phenylpyridinium salts **4**.[a] [a] Reaction conditions: **4** 0.025 M, [Ir]/ligand/*N*-alkyl-2-phenylpyridium bromide = 0.5:0.55:100, 20 h. [b] Yield of the isolated product. [c] Enantiomeric excesses were determined by either SFC or HPLC using a chiral stationary phase. [d] DCE as solvent. [e] DCE/acetone = 5:1 as solvent.

efficient asymmetric catalysis. The unique electronic and structural aspects of the phosphole unit should inform future ligand design for asymmetric catalysis. Further applications of chiral phosphole-based complexes for the asymmetric hydrogenation of heteroarenes and imines are under investigation within our laboratories, and the results will be reported in due course.

Experimental Section

Representative procedure for the asymmetric hydrogenation of pyridinium salts **1**: In a nitrogen-filled glovebox, MP^2-SEGPHOS (4.58 mg, 0.0099 mmol) and [{Ir(cod)Cl}$_2$] (3.07 mg, 0.00457 mmol) were placed into a vial and stirred for 30 min in acetone (7.2 mL). The pyridinium salts **1** (0.05 mmol) were placed into 4 mL hydrogenation vials. About 0.2 mL of the catalyst solution and remaining solvent were added. The vials were placed in a parallel hydrogenation block and after three hydrogen purges, pressurized to 600 psi at 30 °C for 20 h. After carefully releasing the hydrogen, *ee* values were determined by direct sampling of the reaction mixture on SFC or HPLC. Then saturated sodium carbonate was added and the mixture was stirred for 15–30 min. The organic layer was separated and extracted with CH_2Cl_2 twice, and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification was performed by a silica gel column and eluted with hexanes /EtOAc to give desired product **2** or **5**.

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