Communication

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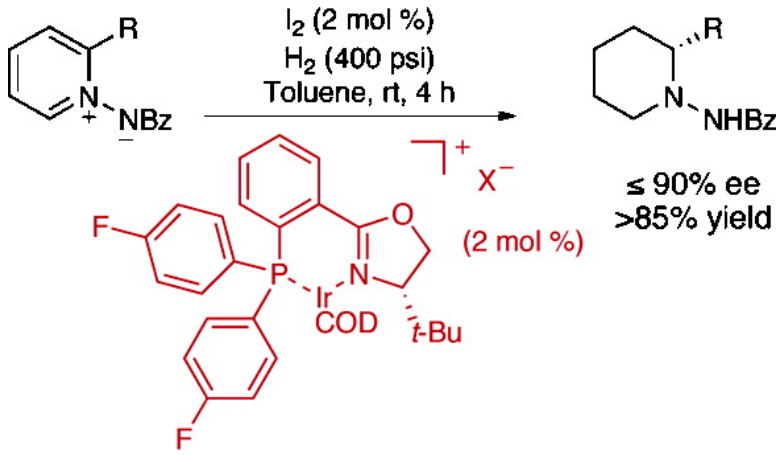

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Catalytic Asymmetric Hydrogenation of *N*-Iminopyridinium Ylides: Expedient Approach to Enantioenriched Substituted Piperidine Derivatives

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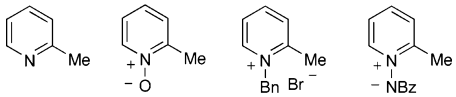
Since the piperidine unit is an extremely important pharmacophore that can be found in many natural and synthetic bioactive compounds, numerous methodologies have been developed to access them.[1] Recently, our group became interested in the asymmetric synthesis of these chiral building blocks using nucleophilic addition to pyridinium salts[2] and *N*-benzoyliminopyridinium ylides.[3] Although the methods are quite successful, the regioselectivity of attack of the nucleophile is critical and can lead to multiple regioisomers.

The wide spectrum of structurally diverse commercially available substituted pyridines and the numerous methods to generate them[4] led us to investigate the asymmetric catalytic hydrogenation of pyridine derivatives to access enantiomerically enriched piperidine derivatives. This has been a long-standing problem in synthesis, and it is only recently that an efficient chiral auxiliary-based method was developed by Glorius.[5,6] Although the asymmetric hydrogenation of quinoline derivatives is feasible in high enantiomeric excesses,[7] the only known examples of catalytic asymmetric hydrogenation of substituted pyridines are rare, limited in scope, and give modest enantioselectivities (<30% ee).[8] In this communication, we wish to report our initial findings on the development of the first highly enantioselective catalytic asymmetric hydrogenation of *N*-acyliminopyridinium ylides.

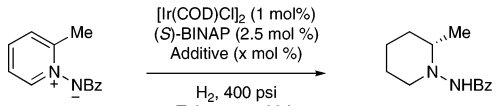
Since the iridium-catalyzed hydrogenation of imines is among the best catalytic system for the reduction of imines,[9] we decided to initially focus our attention on these complexes to test the reactivity of different pyridine derivatives. The preliminary catalyst screening indicated that among compounds **1**−**4**, only pyridinium **4a**[10] was hydrogenated (>95% conversion) upon treatment with H_2 (550 psi) and the iridium catalyst ($[Ir(COD)Cl]_2$ (1.2 mol %), BINAP (2.6 mol %), I_2 (8 mol %), CH_2Cl_2, rt, 20 h).



1 **2** **3** **4a**

As outlined in Table 1, the effect of added iodine is very important in this reaction. We believe it mainly serves as an oxidizing agent to convert an Ir(I) species to the active Ir(III) catalyst. It has been already reported that Ir(III) catalysts are quite efficient in the hydrogenation of imines.[9b,e,f] While TBAI has been previously used as an activator of Ir(I) catalysts,[9c,11] no noticeable improvement in the catalytic activity was observed in our case, indicating that oxidation of the metal is probably initially involved. Replacement of the $[Ir(COD)Cl]_2$ by $[Rh(COD)Cl]_2$ renders the system completely inactive. Attempts at generating directly an active Ir(III) complex from $IrCl_3$ failed. In addition, several other complexes were tested (Ru·BINAP, etc.), and they all proved to be either inactive or not as active.

Table 1. Effect of Additives in the Hydrogenation

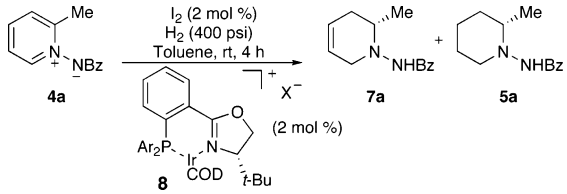


4a **5a**

entry	additive	x (mol %)	conv. (%)[a]	ee **5a** (%)[b]
1	none		24	8
2	TBAI	5	45	8
3	I_2	2	>95 (86)	13
4	I_2	10	94	9
5	I_2	50	<5	

[a] Conversions were determined by ^{1}H NMR; isolated yield shown in parentheses. [b] Enantiomeric excesses were determined by HPLC using a chiral stationary phase. The absolute stereochemistry was determined by derivatization (see Supporting Information for details).

Table 2. Catalyst Optimization[a]



4a **7a** **5a** **8**

entry	Ar (cat.)	conv.(%)[b]	**7a**/**5a**[b]	yield (%)[c]	ee **5a** (%)[d]
1[e]	Ph (**8a**)	>95	9/91	82	68
2	Ph (**8b**)	>95	11/89	89	87
3	*o*-tolyl (**8c**)	10		<5	
4	*p*-OMe (**8d**)	>95	13/87	83	84
5	*p*-F (**8e**)	>95	13/87	>95	90
6	*p*-CF_3 (**8f**)	>95	12/88	>95	81
7	C_6F_5 (**8g**)	59	7/93	20	4

[a] Unless otherwise stated, X = BArF tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. [b] Conversions and ratios were determined by ^{1}H NMR. [c] Yields of **5a** + **7a** determined by ^{1}H NMR using an internal standard. [d] Reported after hydrogenation of **7a** to **5a**. [e] X = Cl.

An extensive screening of different ligands[12] based on the above protocol led to the finding that iridium complexes derived from Pfaltz's[13] phosphinooxazolines (PHOX) ligands proved to be the most promising in terms of enantioselectivities (Table 2, entry 1). However, although the starting materials were completely consumed, the yields of isolated products **5** were highly variable. Our previous work on the addition of nucleophiles to pyridinium ylides[3] and a closer look at the reaction process led us to conclude that the rate of hydrogenation of the dihydropyridine intermediate **6** to tetrahydropyridine **7** was critical to prevent its decomposition and observing high yields for this reaction (Scheme 1).

To resolve this issue, we optimized the catalyst structure by fine-tuning the electronic properties of the phosphine substituents on the ligand and by changing the nature of the counterion of the metal

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Scheme 1

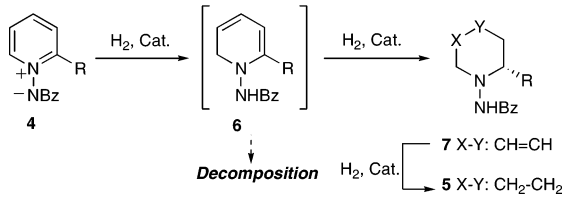
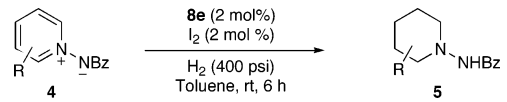


Table 3. Hydrogenation of *N*-Benzoyliminopyridinium Ylides



entry	R	yield **5** (%)[a]	ee **5** (%)[b]	products
1	2-Me	98 (84)	90 (97)	**5a**
2	2-Et	96 (78)	83 (94)	**5b**
3[c]	2-Et	60	78	**5b**
4	2-*n*Pr	98 (75)	84 (95)	**5c**
5	2-Bn	97	58	**5d**
6[c]	2-Bn	65	50	**5d**
7	2-CH_2OBn	85	76	**5e**
8	2-$(CH_2)_3OBn$	88	88	**5f**
9	2,3-Me_2	91 [>95:5]	54	**5g**
10	2,5-Me_2	92 [57/43]	86/84	**5h, 5h′**

[a] Isolated yield after recrystallization is shown in parentheses; diastereomeric ratios are shown in brackets. [b] Determined by HPLC. Enantiomeric excesses after recrystallization are shown in parentheses. [c] Catalyst **8b** was used.

complex (Table 2). We screened a variety of counterions (BF_4, OTf, CF_3CO_2) and found that a cationic species bearing the tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate (BArF) counterion was superior (entries 1 and 2).[14] The use of a bulkier phosphine (entry 3) led to a dramatic decrease of reactivity and almost no conversion. Although the effect on the enantioselectivity was minimal, the use of moderately electron-withdrawing substituents led to an increase in yields (entries 5 and 6), the *p*-fluoro derivative being optimal. However, in all the cases, there is a noticeable amount of remaining tetrahydropyridine **7a** upon reducing **4a**, even with prolonged reaction times. This can be attributed to a slower hydrogenation rate of the isolated double bond and the inactivation of the catalyst by formation of a hydride-bridged iridium trimer.[15]

Using the optimized catalyst and procedure, we proceeded to explore the scope and limitation of the methodology. We submitted different substituted *N*-benzoyliminopyridinium ylides to the hydrogenation conditions, and the results are summarized in Table 3. Although for every substrate the conversions were complete, in some cases, small quantities of the remaining tetrahydropyridine were detected. To avoid this, we proceeded to hydrogenate the crude mixture over Pd/C.[12]

In most cases, the yields obtained are excellent, indicating that a fast and efficient hydrogenation of the key dihydropyridine intermediate takes place. This is in sharp contrast with the results obtained with the unoptimized catalyst **8b** (entries 3 and 6), where a drop in yields and enantioselectivities was observed. These findings clearly demonstrate the importance of the electronic properties of the ligand in this reaction. Pyridinium ylide **4g** afforded only the cis diastereomer, albeit in low enantioselectivities. It appears that the substitution at the 3-position is detrimental to the enantioselectivities with this catalytic system.[16] The low diastereoselectivity observed for substrate **4h**, however, tends to indicate that the enantioselectivity for the hydrogenation of a substituted tetrahydropyridine **7** is low. It is also noteworthy to mention that the reduced products are highly crystalline solids that can easily be enriched by single recrystallization from boiling ethyl acetate (entries 1, 2, and 4). Finally, the hydrogenation adducts obtained can be converted to the corresponding piperidine derivatives by a facile N−N bond cleavage (>85% yield) using either Raney nickel[3,17] or lithium in ammonia.[3,18]

In conclusion, we have developed an efficient catalytic enantioselective hydrogenation of pyridine derivatives. Enhanced reactivity was possible by an optimization of the electronic properties of the catalyst through ligand modification. We are currently investigating the mechanistic aspects of the hydrogenation process as well as improving the scope of the reaction through novel ligand design.

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Supporting Information Available: Experimental procedures and spectral data of selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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