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Stereoselective synthesis of optically active pyridyl alcohols via asymmetric transfer hydrogenation of pyridyl ketones

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Abstract

A chiral Ru(II) complex, RuCl[(*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine](*p*-cymene), serves as an efficient catalyst for asymmetric transfer hydrogenation of 2-acetylpyridine with a substrate to catalyst molar ratio of 200–1000 with HCOOH as a hydrogen source to give (*S*)-1-(2-pyridyl)ethanol in an almost quantitative yield and with 95% ee.

Keywords: asymmetric transfer hydrogenation; formic acid; chiral Ru catalyst; acetylpyridine.

Catalytic asymmetric transfer hydrogenation of ketones or imines using 2-propanol or formic acid as a hydrogen source has been extensively investigated to access optically active alcohols or amines because of its operational simplicity and utilization of a cheap and safe hydrogen source.[1] We have recently developed highly efficient chiral diamine-based Ru(II) catalysts, RuCl(Tsdpen)(η^6-arene) (TsDPEN:*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)[2] and its isoelectronic chiral Rh(III) and Ir(III) catalysts[3] for a practical asymmetric transfer hydrogenation with high enantioselectivity and reactivity. Even benzil or benzoin can be rapidly and stereoselectively reduced with chiral Ru(II) catalysts to optically active hydrobenzoin.[4] The nature of the coordinatively saturated 18 electron chiral Ru(II) catalyst is responsible for the extremely high stereoselectivity in this asymmetric reduction. Thanks to the characteristic properties of chiral Ru catalysts, we found that nitrogen containing ketones such as acetylpyridines or acetylpyrazine are stereoselectively reduced with chiral Ru(II) with formic acid to give the corresponding optically active pyridylethanols or pyrazylethanol with an excellent ee (Scheme 1).

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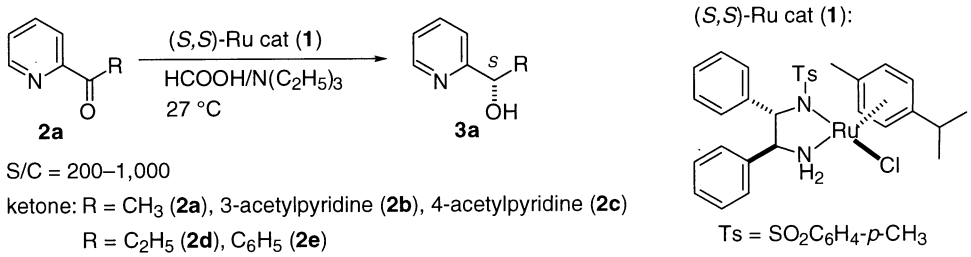


Scheme 1.

Optically active pyridyl alcohols are useful key compounds, not only as pharmaceutical intermediates,[5] but also as useful chiral ligands and auxiliaries in asymmetric synthesis.[6] Although there have been many reports on the synthesis of this important class of compounds by means of asymmetric alkylation to pyridyl aldehydes,[7] stoichiometric or catalytic asymmetric reduction of acetylpyridines,[8,9] enantioselective reduction of *N*-alkylated pyridinium triflate,[10] enzymatic optical resolution of racemic pyridyl alcohols or esters,[11] or deracemization of pyridyl alcohols by enzymes,[12] no practical asymmetric synthetic methods have been reported, except for powerful practical asymmetric hydrogenation catalysts based on Ru–BINAP/chiral diamine complexes.[13]

RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (**1**) has proved to effect asymmetric transfer hydrogenation of 2-acetylpyridine (**2a**) with HCOOH as a hydrogen source, giving (*S*)-1-(2-pyridyl)ethanol (**3a**) with an excellent enantioselectivity. The reaction with a substrate to catalyst molar ratio (S/C) of 200–1000 in a mixture of $HCOOH/N(C_2H_5)_3$ (acetylpyridine:$HCOOH:N(C_2H_5)_3$ molar ratio = 1:4.3:2.5) proceeded smoothly to the product at 27°C in an almost quantitative yield and with up to 95% ee. A chiral Rh complex, Cp*RhCl[(*S*,*S*)-Tscydn] (Cp*:pentamethylcyclopentadienyl, (*S*,*S*)-TsCYDN:(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine)[3] was not effective as a catalyst for the reaction under the same conditions. Table 1 summarizes the experimental results. Increasing the reaction temperature to 50°C caused serious deterioration of the catalyst performance, possibly because of decomposition of the catalyst under these conditions. The product pyridylethanol might replace the chiral diamine ligand to give an inactive catalyst.

The sense of enantioface selection in this asymmetric reduction of the pyridyl ketones was the same as that attained in the reaction of aromatic ketones.[2a] The reaction of 3-acetylpyridine (**2b**) and 4-acetylpyridine (**2c**) with chiral catalyst **1** in a $HCOOH/N(C_2H_5)_3$ mixture under the same conditions described in Table 1 gave (*S*)-1-(3-pyridyl)ethanol (**3b**) and (*S*)-1-(4-pyridyl)ethanol (**3c**) in almost quantitative yields with 89 and 92% ee, respectively. The enantioselectivity decreased in the order of $CH_3>C_2H_5>C_6H_5$ as R groups in the pyridyl ketones. In contrast to the reaction of a benzophenone derivative reported previously,[2d] benzoylpyridine **2e** gave very poor enantioselectivity. These results suggests that the neighboring functional group, the nitrogen atom in this case, must be free from the metal center as observed in asymmetric reduction of benzils or benzoins.[4]

In a similar manner, asymmetric reduction of functionalized acetylpyridine bearing the electron withdrawing group **2f** in CH_2Cl_2 containing a mixture of $HCOOH/N(C_2H_5)_3$ and catalyst **1** at 10°C afforded an optically active pyridylethanol **3f** in almost quantitative yield and with 86% ee, which is an intermediate of PNU-142721, a potent synthetic *anti*-HIV medicine.[5] Its derivative **2g** was reduced slowly to give the corresponding optically active alcohol with the

Table 1
Asymmetric transfer hydrogenation of acetylpryridines catalyzed by chiral Ru(II) catalyst (**1**) with a mixture of $HCOOH/N(C_2H_5)_3$[a]

Ketone	S/C	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[b]	Config.[c]
2a	200	27	12	97	95	*S*[h]
2a	200	50	12	99	91	*S*
2a[d]	200	27	24	24	89	*S*
2a	1000	27	24	91	93	*S*
2a	1000	50	24	14	78	*S*
2b	200	27	24	99	89	*S*[i]
2c	200	27	24	99	92	*S*[j]
2d	200	27	24	100	89	*S*[k]
2e	200	27	24	84	9	*R*[l]
2f[e]	200	10	24	95	86	*S*[m]
2g[e]	200	10	24	36	85	*S*[m]
2h[f]	200	27	24	100[g]	99.6	*S*,*S*[n]

[a] The reaction of pyridyl ketones (2.5 mmol) was carried out with a ketone/$HCOOH/N(C_2H_5)_3$ molar ratio = 1:4.3:2.5.

[b] Unless otherwise noted, yields and ee values were determined by HPLC analysis using a Daicel Chiralcel OD, OJ, Chiralpak AD column or GC analysis using a Chrompak CP-Cyclodextrin-β-236-M-19 capillary column.

[c] Unless otherwise noted, determined from the sign of rotation of the isolated product.

[d] Reaction in 2-propanol, conditions: (*S*,*S*)-Ru cat (**1**) and 1.0 equiv. KO*t*-Bu, ketone:Ru = 200:1, 0.1 M in 2-propanol.

[e] 1.0 M in CH_2Cl_2.

[f] Ketone/$HCOOH/N(C_2H_5)_3$ molar ratio = 1:8.6:5.0.

[g] *dl*:*meso* = 91:9.

[h] $[\alpha]_D$ −27.6 (*c* 0.712, $CHCl_3$) (lit. $[\alpha]_D^{20}$ −26.4 (*c* 1.34, $CHCl_3$), >95% ee (*S*), Ref. 10a).

[i] $[\alpha]_D$ −37.2 (*c* 1.01, CH_3OH) (lit. $[\alpha]_D$ +40.3 (*c* 1.6, CH_3OH), (*R*), Ref. 8c).

[j] $[\alpha]_D$ −39.0 (*c* 0.82, CH_3OH) (lit. $[\alpha]_D^{20}$ −43.0 (*c* 1.24, CH_3OH), >95% ee (*S*), Ref. 10a).

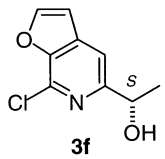
[k] $[\alpha]_D^{28}$ −61.3 (*c* 1.40, CH_3OH) (lit. $[\alpha]_D^{25}$ +38.0 (*c* 1.68, C_2H_5OH), 52.1% ee (*R*), Ohno, A.; Nakai, J.; Nakamura, K.; Goto, T.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3482).

[l] $[\alpha]_D^{28}$ −10.6 (*c* 1.08, $CHCl_3$) (lit. $[\alpha]_D^{25}$ −113.4 (*c* 1.0, $CHCl_3$), 92% ee (*R*), Takemono, M.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 577).

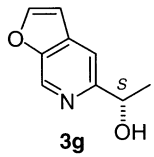
[m] Determined from GLC analysis in comparison to the authentic sample.

[n] $[\alpha]_D^{25}$ −61.0 (*c* 1.9, acetone) (lit. $[\alpha]_D^{25}$ −76.05 (*c* 1.9, acetone) (*S*,*S*), Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, *57*, 5231).

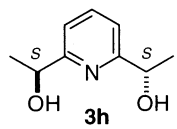
same enantiomeric excess. The reaction of 2,6-diacetylpyridine (**2h**) with a mixture of $HCOOH/N(C_2H_5)_3$ (8.6:5.0) gave an optically active diol with 99.6% ee in 91% yield together with *meso*-diol in 9% yield. This chiral diol can be used as an intermediate of chiral ligands.[14] 2-Acetylpyrazine (**2i**) provided 1-(2-pyrazyl)ethanol (**3i**) in almost quantitative yield with a moderate ee value, 73%.



3f



3g



3h

This paper describes a practical catalytic synthesis of optically active pyridyl alcohols via asymmetric transfer hydrogenation of pyridyl ketones with formic acid as the hydrogen source.[15]

The success of asymmetric reduction of these functionalized ketones is ascribed to the nature of the coordinately saturated diamine-based Ru(II)–arene complexes with excellent carbonyl group discrimination ability, in which the metal/NH bifunctionality makes effective hydrogen transfer possible between ketones and hydrogen donors such as alcohols or formic acid.[2f,16]

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