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Preparation of pyridinyl aryl methanol derivatives by enantioselective hydrogenation of ketones using chiral Ru(diphosphine)(diamine) complexes. Attribution of their absolute configuration by ^{1}H NMR spectroscopy using Mosher's reagent

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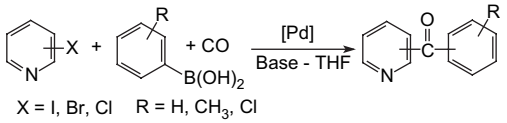
ABSTRACT

Ruthenium–diamine–diphosphine complexes provide highly efficient catalysts for enantioselective hydrogenation of a series of pyridinyl aryl ketones. The hydrogenation proceeds under mild conditions providing chiral pyridinyl aryl methanol derivatives with consistently high yields and moderate to excellent enantioselectivities (up to 99% ee) according to the structure of the chiral diphosphine. NMR studies, based on Mosher's ester derivatisation, allowed to determine the configuration of the major alcohol obtained during asymmetric hydrogenation.

1. Introduction

The conversion of prochiral ketones into enantiomerically pure secondary alcohols is an area of organic synthesis that continues to attract widespread interest due to the importance of this class of alcohols, particularly heterocyclic derivatives, in the field of pharmaceutical, agrochemical and otherwise biologically relevant compounds.[1] Among the various catalytic strategies available for enantioselective reduction of ketones, i.e., hydroboration,[2] hydrosilylation,[3] transfer hydrogenation,[4] alcohol dehydrogenase[5] and hydrogenation,[6] the last one appears the most attractive from atom economy and clean and friendly processes considerations. In this area, a major breakthrough was the discovery by Noyori of the extremely highly efficient ruthenium catalysts of general formula *trans* RuCl(H)(diphosphine)(diamine), which are relevant both in terms of activity and in terms of enantioselectivity.[7] Recently, such catalysts have also been applied successfully in the enantioselective hydrogenation of diaryl ketones and, interestingly, heteroaromatic ketones.[8,9]

In this context, we have recently reported on the palladium catalysed three components cross coupling of pyridine halides, carbon monoxide and boronic acids (carbonylative Suzuki coupling) as a straightforward access to a diversity of pyridinyl aryl ketones (Scheme 1).[10]



Scheme 1. Synthesis of pyridinyl aryl ketones via carbonylative Suzuki coupling.

This class of ketones furnishes interesting substrates for asymmetric hydrogenation into pyridinyl aryl methanol derivatives. Here, we report on the enantioselective hydrogenation of a series of pyridinyl aryl ketones performed in the presence of Noyori type catalysts and on the determination of the configuration of the prevalent hydroxy products.

2. Results and discussion

Various chiral diamines and atropisomeric diphosphines have been combined with success on ruthenium and used in asymmetric hydrogenation of simple ketones with very high substrate/catalyst (S/C) ratios.[6a] In particular, the diamine DAIPEN and the diphosphines of the BINAP family provide excellent chiral auxiliaries for

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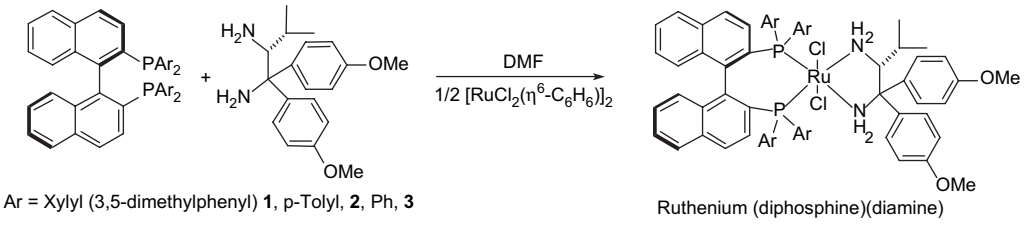


Scheme 2. Synthesis of ruthenium precatalysts.

highly selective ruthenium hydrogenation catalysts applicable to a large array of ketonic substrates.[8] The hydrogenation of some pyridinyl aryl ketones has already been described.[9] Basically, only one catalytic system based on Ru–XylBINAP–DAIPEN has been reported. For our study, we have chosen to combine (*R*)-DAIPEN and three BINAP's, i.e., (*R*)-XylBINAP, (*R*)-*p*-TolBINAP and (*R*)-BINAP in order to investigate the influence of the substituents on the phenyl residues on the phosphorous atoms of the chiral auxiliary. Thus, we prepared the corresponding ruthenium precatalysts **1**–**3** following reported procedures (Scheme 2).[4b] The first attempts of hydrogenation were carried out on phenyl pyridinyl methanone **4a** as a model substrate while varying the substrate/catalyst (S/C) ratios and the chiral diphosphine (Scheme 3).

The results are reported in Table 1. The first experiment carried out with precatalyst **1** at a low S/C ratio in the presence of KOH showed the efficiency of the catalytic system as the hydroxy product was obtained quantitatively with 70% ee (entry 1). In the absence of molecular hydrogen, the conversion reached only 2% after 40 h showing that the transfer hydrogenation is a minor process in the catalytic conditions (entry 2).[6a] At a higher S/C ratio (S/C=1000), a conversion of 50% and an enantioselectivity of 70% ee were obtained within 0.5 h with the same catalyst (entry 3). When increasing further the S/C ratio the process became sluggish (entry 4). Lowering the reaction temperature to 0 °C led to the improvement of the enantioselectivity to 80% ee but the reaction rate decreased significantly (entry 5). Precatalyst **2** provided a less selective catalyst than **1** (entry 6 vs 3). Performing the hydrogenation under atmospheric pressure of molecular hydrogen induced a markedly decrease of the reaction rate but has no influence on the enantioselectivity (compare entries 6 and 7). Finally, among the three diphosphine used, XylBINAP appeared the most appropriate for the hydrogenation of **4a** (70–80% ee) (entries 1, 3, 5, 6–8).

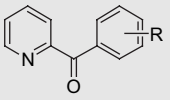
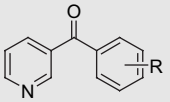
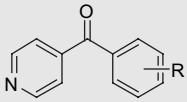
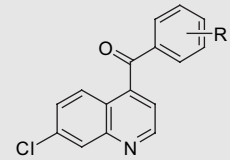
We then examined the hydrogenation of a series of pyridinyl aryl methanones prepared via carbonylative Suzuki coupling[10] in the presence of the three precatalysts **1**–**3**. The results are summarised in Table 2. Despite structural similarities, the substrates proved to behave differently under the hydrogenation conditions and no general stereoelectronic trend could be deduced from these results. Nevertheless, we observed that BINAP based catalysts are affording commonly lower selectivities (8–42% ee) than those bearing XylBINAP or *p*-TolBINAP. Still, one substrate, **5b**, was hydrogenated with 93% ee in the presence of BINAP (entry 6). In addition, we can roughly estimate that aryl ketones bearing pyridin-3-yl moieties (**5a**–**5d**, entries 5–8) were hydrogenated with higher selectivities than their homologues with pyridin-2-yl (**4a**–**4d**, entries 1–4) and pyridin-4-yl (**6a**, entry 9) or chloroquinoline (**7a**–**7c**, entries 10–12) residues.

Table 1
Asymmetric hydrogenation of **4a**[a]

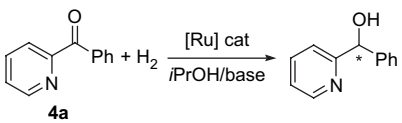
Entry	Time (h)	[Ru][b]	S/C	Conv[c] (%)	ee[d] (%)	TOF (h^{-1})
1	15	**1**	100/3	100	70	—
2	40	**1**	100/3	2[e]	nd	—
3	0.5	**1**	1000/1	50	70	1000
4	0.5	**1**	10,000/1	2	nd	400
5	2	**1**	1000/1	10[f]	80	50
6	1	**2**	1000/1	99	33	990
7	4	**2**	1000/1	11[g]	33	27.5
8	1	**3**	1000/1	81	14	810

[a] General conditions: **4a**=0.1 mmol, KOH/[Ru]=5/1, *i*-PrOH: 3 mL, 30 °C, P_{H2}=20 bar.
[b] Ruthenium precatalysts.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC on a Chiralpack AD column.
[e] Reaction carried out without H_2 under 20 bar of N_2.
[f] Reaction carried out at 0 °C.
[g] Reaction performed under 1 bar of H_2.

Table 2
Hydrogenation of pyridinyl aryl methanones[a]

Entry	Ketone	R	Cata. product	**3** ee[b] (%)	**2** ee[b] (%)	**1** ee[b] (%)
1		**4a** H	**8a**	14	33	70
2		**4b** *o*-CH_3	**8b**	20	34	99
3		**4c** *p*-CH_3	**8c**	8	40	60
4		**4d** *m*-Cl	**8d**	15	9	50
5		**5a** H	**9a**	41	50	69
6		**5b** *o*-CH_3	**9b**	93	79	−68[c]
7		**5c** *p*-CH_3	**9c**	42	50	78
8		**5d** *m*-Cl	**9d**	19	24	55
9		**6a** H	**10a**	17	32	54
10		**7a** H	**11a**	31	3	90
11		**7b** *o*-CH_3	**11b**	20	25	−13[c]
12		**7c** *p*-CH_3	**11c**	12	−25[c]	−80[c]

[a] General conditions: ketone=1 mmol, ketone/KOH/[Ru]=1000/5/1, *i*-PrOH: 3 mL, 30 °C, P_{H2}=20 bar. All conversions were >99% as determined by ^{1}H NMR. The pure alcohols were isolated after silica gel chromatography in good yields (80–95%).
[b] Enantiomeric excess (ee) determined by HPLC on Chiralpack AD column. Determination of the configuration, see text.
[c] A negative ee indicate that the opposite enantiomer is formed preferentially.



Scheme 3. Hydrogenation of phenyl pyridinyl methanone **4a**.

Compared to the catalyst modified by BINAP (obtained from **3**), the more sterically demanding complex **2** $RuCl_2$[(*R*)-DAIPEN][(*R*)-*p*-TolBINAP] led generally to a catalyst exhibiting slightly better enantioselectivities (Δee=+5 to +32%) with the exception of hydrogenation of **4d** (entry 4), **5b** (entry 6), **7a** (entry 10) for which the enantioselectivity dropped significantly (Δee=− 6, −14 and −29%,