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Preparation of tricyclic imidazopyridines by asymmetric ketone hydrogenation in the presence of ruthenium phosphino-oxazoline catalyst

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Abstract—The asymmetric hydrogenation of the prochiral heterocyclic ketone **2** and its O-protected analogues **9** to **11** in the presence of the ruthenium POX catalyst $RuCl_2(PPh_3)(Ph_2P\text{-}Fc\text{-}oxa^iPr)$ was studied. The reactivity of the substrate and the enantioselectivity of the reduction depended on the nature of the protecting group. The best results were achieved with the thexyldimethylsilyl protecting group: The corresponding alcohol **13** was obtained in 86% yield and 88% ee and constitutes a valuable intermediate for the synthesis of the potassium-competitive acid blocker BYK 311319 **1**.

1. Introduction

Acid related diseases, such as gastroesophageal reflux disease (GERD) and peptic ulcer disease, have a high prevalence and represent a large economic burden.[1–3] The reduction of acid secretion by inhibition of the gastric proton pump enzyme (H^+/K^+-ATPase) constitutes an effective approach for the treatment of these medical conditions.[1–3] With the introduction of proton pump inhibitors (PPis), which inhibit the H^+/K^+-ATPase in an irreversible manner, highly effective therapeutic agents have become available. Despite the clear success of PPis, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or tenatoprazole, several pharmaceutical companies are currently engaged in the development of potassium-competitive acid blockers (P-CABs). Due to their new mode of action (reversible inhibition of H^+/K^+-ATPase), P-CABs might be able to overcome some limitations encountered during the treatment with PPis.[4–7]

Over the course of our P-CAB led optimization program, we identified the tricyclic imidazo[1,2-*a*]pyridine BYK 311319 **1** as a potent inhibitor of the H^+/K^+-ATPase showing promising pharmaceutical activity.[8,9] A key step in the synthesis of the enantiopure P-CAB **1** is the asymmetric reduction of ketone **2** and subsequent Mitsunobu cyclization of the resulting diol **3** (Scheme 1).[8,9]

A variety of methods for the asymmetric reduction of ketones are currently available, including enzymatic transformations,[10] hydrosilylation,[11,12] hydroboration,[13–16] transfer hydrogenation,[17,18] and hydrogenation.[19,20] In the field of enantioselective homogeneous hydrogenation, the Noyori Ru-PP-NN systems of the type $RuCl_2$[diphosphine][diamine] in the presence of base constitute the most prominent (pre)catalysts and excellent results have been published for aromatic ketone substrates in recent years.[19,20] Consequently, one of the most active and selective catalysts, $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] **4**, was tested in the presence of potassium *tert*-butylate for the asymmetric hydrogenation of **2**. Under optimized conditions and using an S/C ratio of 130:1, chiral alcohol **3** could be prepared with an enantiomeric purity of 85% ee.[8,9] While this result was encouraging, we were still aiming at the identification of an alternative, more selective system for the asymmetric reduction of ketone **2**. Herein we report the preparation of alcohol **3** using the ruthenium POX (phosphino-oxazoline) catalyst system $RuCl_2(PPh_3)(Ph_2P\text{-}Fc\text{-}oxa^iPr)$ **5** depicted in Figure 1.[21–24] Upon activation with base, complexes of the type $RuCl_2(PPh_3)$(aminophosphine)

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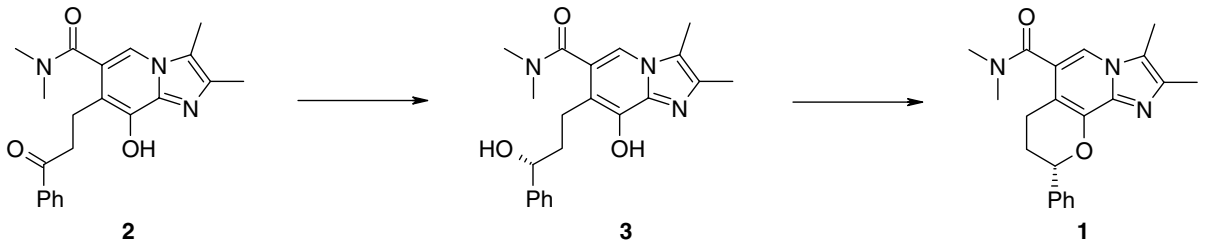


Scheme 1.

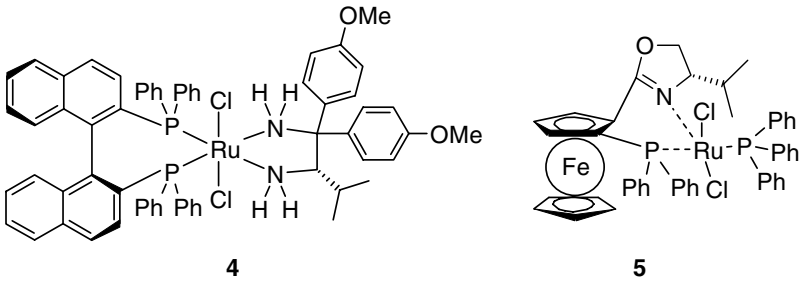


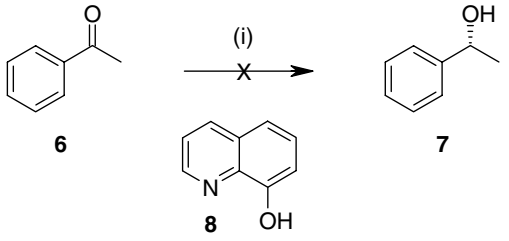
Figure 1. Structure of the hydrogenation catalysts $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] **4** and $RuCl_2(PPh_3)(S_C,S_m)$-(Ph_2P-Fc-oxa^{i}Pr) **5**.

are productive and selective catalysts for a range of different substrates.

2. Results and discussion

First, we investigated the asymmetric reduction of ketone **2** in the presence of precatalyst **5** and either sodium hydroxide or potassium *tert*-butylate as base. Since in neither case significant conversion was observed, it was envisaged that the free phenol moiety of ketone **2** might interfere with catalysis. This hypothesis was corroborated by test experiments: acetophenone **6** was hydrogenated using complex **5** and sodium hydroxide as a base in toluene. These conditions usually allow for full conversion at S/C ratios of up to 50,000:1 and (1*R*)-1-phenylethanol **7** is obtained with an enantiomeric purity of >98% ee.[22–24] When this hydrogenation was carried out, however, at S/C = 100:1 in the presence of 1 mol % of 8-hydroxychinoline **8**, no conversion of acetophenone **6** was observed (Scheme 2).

Presumably, the coordination of the phenol moiety and the neighbouring aromatic nitrogen of substrate **2** (or the respective functionalities in 8-hydroxychinoline **8**) to ruthenium effectively block catalyst activity. Better results can be obtained with protected substrates and, consequently, phenolic ketone **2** was transformed into the corresponding benzyl ether **9**, silyl ether **10**, or pivaloyl ester **11**, respectively (Scheme 3).

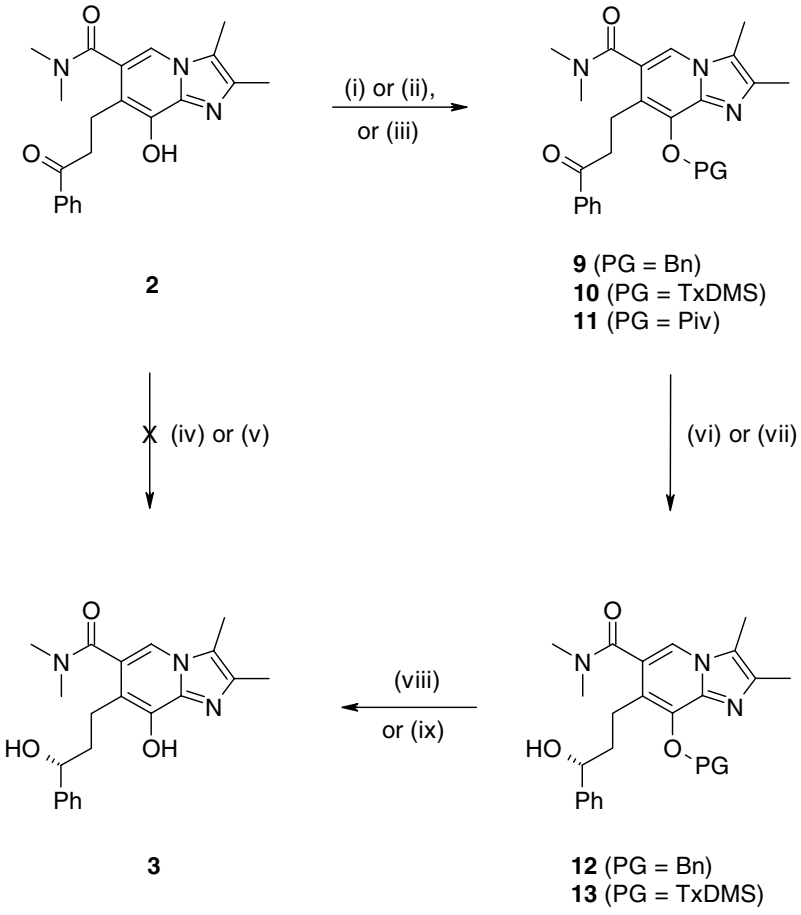


Scheme 2. Reagents and conditions: (i) 1 mol % $RuCl_2(PPh_3)(Ph_2P$-Fc-oxa^{i}Pr), 1 mol % **8**, NaOH, toluene, H_2O, H_2, no conversion.

The asymmetric reduction of the *O*-benzyl-protected ketone **9** in the presence of POX catalyst **5** was studied first. On a 0.5 mmol scale, the reaction was feasible at substrate to catalyst ratios (S/C ratios) of up to 200:1 (Table 1, entries 1–3). Quantitative conversion of the starting material **9** was observed and the corresponding alcohol **12** was formed selectively with an enantiomeric purity of 83% ee. The hydrogenation reaction could be conducted at either 40 °C or at room temperature, showing no effect on the ee value (entries 2 and 3). At an S/C ratio of 300:1, the conversion was incomplete (70%), whereas the enantiomeric purity remained unchanged (83% ee, entry 4). On a 5 mmol scale, the reduction of ketone **9** was run at a higher dilution in the presence of more hydrogenation catalyst and base (entry 5). Quantitative conversion of the starting material **9** occurred within a period of three days and the benzyl-protected alcohol **12** was isolated in 96% yield with an enantiomeric purity of 78% ee.

For reasons of comparison, we also conducted a preliminary experiment of the reduction of ketone **9** in the presence of Noyori catalyst **4** (Scheme 3): hydrogenation using 1 mol % of $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] and potassium *tert*-butylate afforded alcohol **12** in 79% yield and 75% ee.

Although the observation of hydrogenation activity for the benzyl protected substrate **9** proved the assumption of the phenol group acting as a catalyst deactivator for Ru-POX



Scheme 3. Reagents and conditions: (i) preparation of **9**: K_2CO_3, BnCl, DMF, 55 °C, 5 h, 96%; (ii) preparation of **10**: TxDMSCl, imidazole, DMF, rt, 1 h, 94%; (iii) preparation of **11**: PivCl, K_2CO_3, acetone, rt, 2 h, 69%; (iv) 2 mol % $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$, NaOH, toluene, H_2O, 80 bar H_2, 80 °C, 24 h, <5% conversion; (v) 2 mol % $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$, KO^tBu, 2-PrOH, 80 bar H_2, rt, 66 h, <5% conversion; (vi) $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$, NaOH, toluene, H_2O, see Table 1; (vii) reduction of **9**: 1 mol % $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN], KO^tBu, 2-PrOH, 40 bar H_2, rt, 22 h, 79%, 75% ee; (viii) cleavage of benzyl protecting group: Pd/C, 1,4-cyclohexadiene, EtOH, 80 °C, 2 h, 83%; (ix) cleavage of silyl protecting group: TBAF, THF, rt, 5 h, 86%.

Table 1. Asymmetric reduction of O-protected ketones **9**, **10**, and **11** in the presence of $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$ **5**

Entry	SM	Scale (mmol)	S/C ratio	Toluene (ml)/1 N NaOH (ml)	Conditions	Conversion[d] (%)	ee[d,e] (%)
1	**9**	0.5	100:1	3/1	80 bar H_2, 40 °C, 18 h[a]	100	83
2	**9**	0.5	200:1	3/1	80 bar H_2, 40 °C, 15 h[a]	100	83
3	**9**	0.5	200:1	3/1	80 bar H_2, rt, 16 h[a]	100	83
4	**9**	0.5	300:1	3/1	80 bar H_2, rt, 16 h[a]	70	83
5	**9**	5.0	20:1	180/60	80 bar H_2, 40 °C, 3 d[b]	100	78
6	**10**	0.5	100:1	3/1	80 bar H_2, 40 °C, 16 h[a]	100	90
7	**10**	0.5	200:1	3/1	80 bar H_2, 40 °C, 17 h[a]	100	89
8	**10**	0.5	400:1	3/1	80 bar H_2, 40 °C, 16 h[a]	90	90
9	**10**	0.5	400:1	3/1	40 bar H_2, 40 °C, 22 h[a]	100	90
10	**10**	1.0	400:1	5/2	80 bar H_2, 40 °C, 16 h[c]	100	90
11	**10**	0.5	400:1	3/0.5	80 bar H_2, 40 °C, 16 h[a]	33	90
12	**10**	0.5	500:1	2/1	80 bar H_2, 40 °C, 65 h[a]	67	88
13	**10**	0.5	500:1	2/1	80 bar H_2, rt, 65 h[c]	80	89
14	**10**	1.0	500:1	5/2	80 bar H_2, 40 °C, 67 h[c]	78	90
15	**10**	5.0	20:1	180/60	80 bar H_2, 40 °C, 3 d[b]	100	88
16	**11**	0.5	200:1	4/1	80 bar H_2, 40 °C, 66 h[a]	<5	—

[a] 50 ml autoclave with stirring bar.
[b] 1 l autoclave with glass inlay.
[c] 50 ml TOP autoclave (magnet driven propeller stirrer).
[d] Determined by chiral HPLC.
[e] Absolute configuration of **12** and **13**: (*R*) (see Refs. 8 and 9).

type systems, stereoselectivities still remained lower than obtained for the unprotected ketone starting material. Therefore, we turned our attention toward the asymmetric hydrogenation of the silyl-protected ketone **10** in the presence of ruthenium POX catalyst **5**. Again, quantitative conversion of the starting material **10** was observed at S/C ratios of 100:1 and 200:1 (Table 1, entries 6 and 7). To our delight, the silyl-protected alcohol **13** was obtained in better enantiomeric purity than its benzyl-protected analogue **12** (90% ee vs 83% ee). At an S/C ratio of 400:1, the reduction of ketone **10** still proceeded smoothly and with high enantioselectivity. The reduction could be conducted at hydrogen pressures of 80 bar (entry 8) or 40 bar (entry 9). At these low catalyst concentrations, the use of propeller-stirring enabling more efficient hydrogen mixing in comparison to magnetic stirring seemed to be advantageous (entry 10). The stoichiometry of base is crucial for the outcome of the hydrogenation reaction: In the presence of 1 equiv of the base, only 33% conversion was obtained (entry 11), whereas the reduction proceeded in a nearly quantitative manner, when 2 equiv of base were employed (entries 8–10). At an S/C ratio of 500:1, the conversion of starting material **10** did not exceed 80% even after an extended reaction period of three days (entries 12–14). Again, the use of propeller-stirring (entries 13 and 14) was beneficial, whereas little effect on conversion and ee was observed by employing slightly different concentrations and reaction temperatures. The reduction of silyl-protected ketone **10** was also feasible on a 5 mmol scale. Due to the higher dilution of substrate **10**, more hydrogenation catalyst and base was employed (entry 15). The corresponding alcohol **13** was isolated in 86% yield and possessed an enantiomeric purity of 88% ee.

Subsequently, the pivaloyl-protected ketone **11** was examined as a potential substrate for the asymmetric hydrogenation in the presence of $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$ **5**. Unfortunately, no transformation of the starting material occurred when applying the standard reaction conditions (Table 1, entry 16). This observation can be explained with partial cleavage of the pivaloyl protecting group releasing ketone **2**. Since the catalyst system seems to be sensitive toward minor phenolic impurities, even the presence of small amounts of ketone **2** could result in the deactivation of the hydrogenation catalyst.

Finally, diol **3** was prepared from its O-protected precursors **12** and **13**. The benzyl ether **12** was cleaved by catalytic transfer hydrogenation, whereas the thexyldimethylsilyl protecting group was removed by treatment of compound **13** with TBAF (Scheme 3). BYK 311319 **1** was obtained from diol **3** by Mitsunobu cyclization as described previously.[8,9,21]

3. Conclusion

In conclusion, we have demonstrated that the Ruthenium POX catalyst system $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$ **5** provides a valuable alternative to the Noyori catalyst $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] **4**. Whereas the asymmetric reduction with Noyori's catalyst **4** can be performed with the unprotected ketone **2** or in the presence of a protecting group, protection of the phenol moiety is crucial for the successful hydrogenation using ruthenium POX catalyst **5**. Hydrogenation of the *O*-benzyl- and the *O*-thexyldimethylsilyl protected ketones **9** and **10** in the presence of $RuCl_2(PPh_3)(Ph_2P\text{-Fc-oxa}^iPr)$ **5** afforded chiral alcohols **12** and **13** in excellent yields and good enantiomeric purities. Additional fine-tuning of the reaction conditions is currently in progress and should lead to increased catalyst performance. Furthermore, since the enantioselectivity tends to depend on the type of protecting group used, the examination of different protecting groups might also be promising.

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