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Preparation of tricyclic imidazopyridines by asymmetric ketone hydrogenation in the presence of $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN]

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ABSTRACT

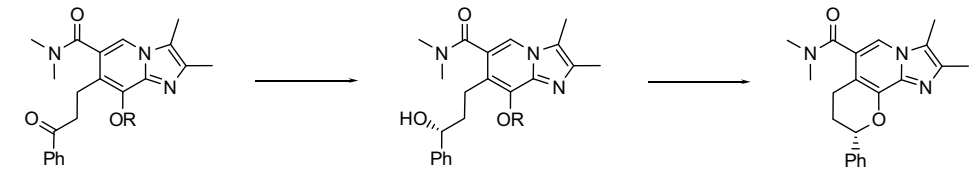
The novel complex $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] was identified as a highly active catalyst for the asymmetric reduction of a variety of prochiral ketones possessing an imidazo[1,2-*a*]pyridine scaffold. The corresponding alcohols were obtained in excellent enantiomeric purities (>96% ee) and served as valuable intermediates for the synthesis of pharmacologically active 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines. The complexity of these multi-functional substrates required the development of specific reaction conditions. Whereas the reduction with $RuCl_2$[PP][NN] catalysts (Noyori catalysts) has never been reported to occur under aqueous conditions, in the present case, the use of aqueous isopropanol or *tert*-butanol was not only tolerated, but also turned out to be beneficial, especially when the reduction was conducted at high substrate to catalyst (S/C) ratios.

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 the 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 became available. Despite the clear success of PPis, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or tenatoprazole, several pharmaceutical companies are 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 of the limitations encountered during the treatment with PPis.[4–7]

Over the course of our P-CAB lead 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).[8–11]

Out of the many methods that are available for the asymmetric reduction of ketones, for example, enzymatic transformations,[12] hydrosilylation,[13,14] hydroboration,[15–18] transfer hydrogenation,[19,20] and hydrogenation,[21,22] we first focused on the catalytic hydrogenation reaction described by Noyori et al.[8,9] In a typical experimental procedure for this methodology, the carbonyl derivative is dissolved in isopropanol and hydrogenated in the



Scheme 1.

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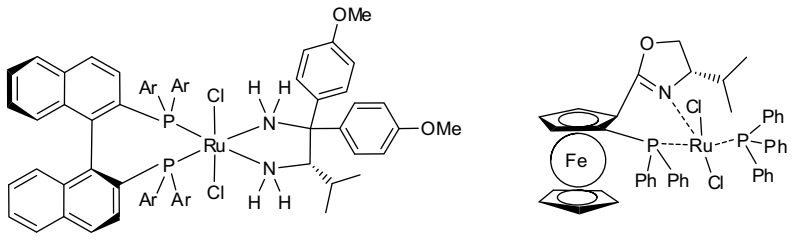
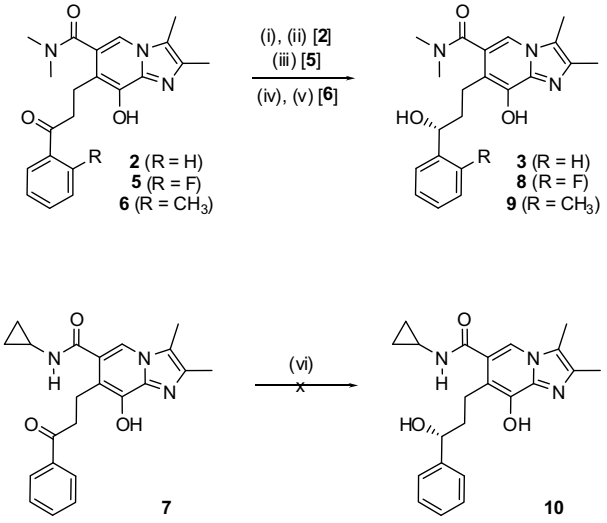


4 (Ar = Ph), **11** (Ar = 3,5-xylyl) **12**

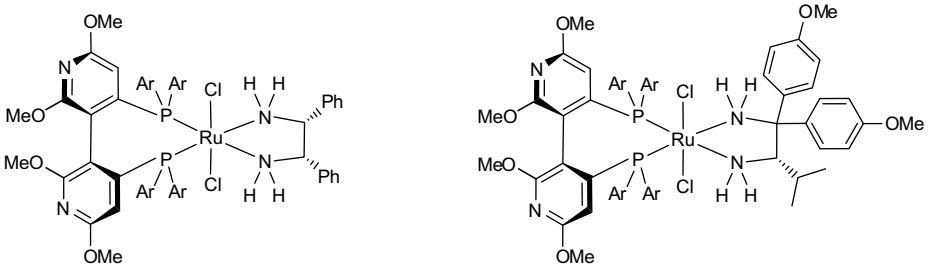
Figure 1. Available hydrogenation catalysts for the reduction of ketone **2**.

presence of a base and a homogeneous catalyst, which might be formed in situ from a ruthenium precursor containing an optically active bis(diarylphosphane) ligand ([PP], e.g., [(*S*)-BINAP]) and an optically active diamine ([NN], e.g., (*S*,*S*)-DPEN).[23–26] In modification of this procedure, the in situ generated catalytic system is replaced by a pure ruthenium complex of the generic formula $RuCl_2$[PP][NN]. The use of a preformed catalyst complex offers several advantages, such as increased reaction rates, higher productivity, and increased stability against air and moisture.[27] Consequently, one of the most active and selective catalysts, $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] **4** (Fig. 1),[23,28] 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, the chiral alcohol **3** could be prepared with an enantiomeric purity of 85% ee.[8,9] While this result was encouraging, we found complex **4** to be significantly less active in the transformation of structurally related ketones, for example, derivatives **5** and **7**. The corresponding alcohols **8** and **10** were, if at all, obtained in low enantiomeric purity (Scheme 2).[29] The use of another highly active Noyori catalyst $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] **11** (Fig. 1)[23] allowed us to achieve the reduction of substrate **2** with full conversion at S/C 100/1 in >95% ee but, when the same catalyst was applied to the reduction of the more challenging analogue **6**, the enantioselectivity dropped to 73% ee (Scheme 2).[29]



Scheme 2. Reagents and conditions: (i) 1 mol % **11**, 1.1 equiv KO^{t}Bu, 2-PrOH, *t*-BuOH, 10 bar H_2, 50 °C, 24 h, 100% conversion, >95% ee; (ii) 1 mol % **17**, 1.1 equiv KO^{t}Bu, 2-PrOH, *t*-BuOH, 10 bar H_2, 30–50 °C, 24–30 h, 100% conversion, 59–63% ee; (iii) 2 mol % **4**, 1.1 equiv KO^{t}Bu, 2-PrOH, 40 bar H_2, rt, 2 × 23 h, 25% **5**, 63% **8** (39% ee); (iv) 0.8 mol % **11**, 1.2 equiv KO^{t}Bu, 2-PrOH, *t*-BuOH, 25 bar H_2, 70 °C, 20 h, >95% conversion, 72% **9** (73% ee); (v) 0.5 mol % **17**, 1.2 equiv KO^{t}Bu, 2-PrOH, *t*-BuOH, H_2O, 25 bar H_2, 65 °C, 16 h, 64% conversion; (vi) 2.2 mol % **4**, 1.1 equiv KO^{t}Bu, 2-PrOH, 40 bar H_2, rt, 22 h, 80% of starting material **7** recovered.

We therefore decided to extend our investigations in the field of Noyori catalysts and to focus on complexes $RuCl_2$[PP][NN], where the ligand [PP] does not constitute an enantiomerically pure (substituted) BINAP derivative. The ligands that are currently available for asymmetric hydrogenation have already been covered in several review articles.[21,30] The synthesis of ligands of the P-Phos family[31] and their application for the asymmetric reduction of carbonyl compounds were described by Chan et al. and they appeared to be of special interest to us.[32–34] In the presence of catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*,*S*)-DPEN] **17** (Fig. 2),[23,31] a wide variety of aromatic and heteroaromatic ketones were hydrogenated with excellent enantioselectivities. While Chan had reported the highly



17 (Ar = 3,5-xylyl) **18** (Ar = 3,5-xylyl)

Figure 2. Structure of the hydrogenation catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*,*S*)-DPEN] **17** and $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**.

efficient use of this complex, we found that this catalyst gave full conversion but only moderate enantioselectivity (59–63% ee) in the reduction of substrate **2** (R = H) under standard literature conditions (Scheme 2).[29] Even less encouraging results were obtained for ketone **6** (R = CH_3), where the hydrogenation in the presence of 0.5 mol % of complex **17** stalled at 64% conversion.[29] This prompted us to prepare the catalyst $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18** (Fig. 2), which has not been reported before, and to investigate its use as hydrogenation catalyst for the asymmetric reduction of ketone **2** and structurally related ketones, for example, the substrates **5**–**7**.[35]

2. Results and discussion

2.1. Development of a highly efficient method for the asymmetric reduction of ketone 2

Our first experiments were aimed at the identification of suitable reaction solvents and the estimation of a feasible S/C-ratio. To this end, we investigated the asymmetric reduction of ketone **2** in a Biotage Endeavour apparatus (8 × 12 ml parallel reactors with overhead stirring and block heating). In the course of our investigations, we used two experimental set-ups that gave identical results (see Ref. 36 and Section 4). The results are summarized in Table 1.

When 2-propanol was used as a solvent, full conversion to the alcohol **3** occured at S/C ratios of 100:1 and 250:1 (entries 1 and 4). Under these reaction conditions, the hydrogenation proceeded in a homogeneous medium, that is, the potassium salt of the substrate and the product were soluble in the reaction medium. At an S/C ratio of 500:1, the conversion dropped to 67% (entry 7). When DMF was added as a co-solvent, a significant reduction in catalyst activity was observed (entries 2 and 6). On the other hand, the reaction went to completion in wet 2-propanol (entry 3). This was a rather surprising finding, since this class of hydrogenation catalysts usually requires anhydrous conditions. We investigated this phenomenon more systematically and found that (almost) complete transformation of ketone **2** occurred even when 5% (entries 8 and 11) or 15% (entry 5) of water was added as a co-solvent. Moreover, the presence of water seemed to be beneficial at high S/C ratios affording significant conversion even at 800:1 and 1000:1 (entries 11 and 12). The use of other alcoholic solvents was also tested. Low conversion, however, was obtained with ethanol (entry 9) while no conversion was obtained in methanol (entry 10). One reduction (entry 13) was performed in the presence of a greater excess of base. The hydrogenation seemed to proceed faster than the reaction described in entry 12, which was run in the presence of 1.1 equiv of base under otherwise identical conditions.

In the first instance, the optimization of the reaction conditions at S/C = 1000:1 focused on three parameters: temperature, base concentration, and the presence of water. Substance concentration and pressure were kept constant (0.125 M, 10 bar H_2). Based on the data presented in Table 2, the following conclusions can be drawn: first, the use of water as a co-solvent is highly beneficial and produces an increase in both conversion and enantioselectivity (compare entries 1 and 5, 2 and 6, 3 and 7, 4 and 8). Second, temperatures above 70 °C cause a reduction in the overall reactivity of the catalyst, presumably due to catalyst decomposition (compare entries 2 and 4, 5 and 7). Third, the use of larger amounts of base in the reaction possibly produces an increase in conversion but at the expense of some erosion in enantioselectivity (compare entries 1 and 2, 7 and 8).

The use of higher pressure was next tested using a mixture of 2-propanol and water as solvent and 1.1–1.2 equiv of potassium *tert*-butylate as base (entries 9 and 10). As expected from previous experiences with Noyori-type catalysts,[37] this was highly benefi-

Table 1
Asymmetric reduction of ketone **2** with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**: solvent screening and estimation of feasible S/C-ratio; reaction conditions: 10 bar H_2 pressure, 70 °C, 16 h

Entry	S/C	Equiv KO^{t}Bu[a]	Solvent ratio			Concd (M)	Conv.[b] (%)
			2-PrOH	*t*-BuOH	Other		
1	100:1	1.1	86	14	—	0.125	100[c]
2	100:1	1.1	61	14	25 (DMF)	0.125	30
3	100:1	1.1	86	14	Wet (H_2O)	0.125	100
4	250:1	1.1	86	14	—	0.125	100
5	250:1	1.1	71	14	15 (H_2O)	0.125	96
6	250:1	1.1	61	14	25 (DMF)	0.125	<10
7	500:1	1.1	86	14	—	0.125	67
8	500:1	1.1	81	14	5 (H_2O)	0.125	100
9	500:1	2.2	—	18	82 (EtOH)	0.083	26
10	500:1	2.2	—	18	82 (MeOH)	0.083	No conv.
11	800:1	1.1	81	14	5 (H_2O)	0.125	98
12	1000:1	1.1	86	9	5 (H_2O)	0.086	72
13	1000:1	1.65	84	11	5 (H_2O)	0.086	92

[a] A 1 M solution of KO^{t}Bu in *t*-BuOH was employed.
[b] The conversion was determined by HPLC.
[c] The hydrogenation uptake curve shows that the transformation was complete in 4–5 h.

Table 2
Asymmetric reduction of ketone **2** with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**: influence of temperature, base concentration, presence of water and pressure; reaction conditions: S/C = 1000:1, 16–20 h, substrate concentration 0.125 M

Entry	Equiv KO^{t}Bu[a]	Solvent ratio			Temp. (°C)	Pressure (bar)	Conv.[b] (%)	ee[b] (%)
		2-PrOH	*t*-BuOH	H_2O				
1	1.1	86	14	—	70	10	39	86
2	2.2	72	28	—	70	10	70	45
3	1.1	86	14	—	80	10	27	71
4	2.2	72	28	—	80	10	34	70
5	1.1	81	14	5	70	10	87	85
6	2.2	67	28	5	70	10	80	85
7	1.1	81	14	5	80	10	55	97
8	2.2	67	28	5	80	10	75	73
9	1.1	81	14	5	70	30	96	97
10	1.1	81	14	5	60	30	96	98

[a] A 1 M solution of KO^{t}Bu in *t*-BuOH was employed.
[b] Conversion and enantioselectivity were determined by HPLC.

Table 3
Asymmetric reduction of ketone **2** with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**: influence of substrate concentration; reaction conditions: 20–25 bar H_2 pressure, 65 °C, 16–18 h

Entry	S/C	Concd (M)[a]	Equiv KO^{t}Bu[b]	Solvent ratio			Time (h)[c]	Conv.[d] (%)	ee[d] (%)
				2-PrOH	*t*-BuOH	H_2O			
1	750:1	0.25	1.1	63	27	10	n.d.	100	>98
2	750:1	0.5	1.1	35	55	10	n.d.	100	>98
3	750:1	0.5	1.1	—	90	10	~7	100	>98
4	1000:1	0.25	1.1	63	27	10	~10	100	>98
5	1000:1	0.5	1.1	35	55	10	~6	100	>98
6	1000:1	0.67	1.1	—	73	27	n.d.	38	>98
7	1000:1	0.5	1.8	—	90	10	n.d.	86	91
8	1000:1	0.67	1.1	17	73	10	~5	100	>98
9	1500:1	0.5	1.1	35	55	10	~6–8	100	>98
10	1500:1	0.5	1.1	45	55	—	~16	60	48
11	2500:1	0.67	1.1	17	73	10	~6	100	>98
12	2500:1	0.67	1.1	—	90	10	~6	100	>98

[a] The maximum concentration of 0.67 M was determined by the use of a 1 M solution of KO^{t}Bu in *t*-BuOH.
[b] A 1 M solution of KO^{t}Bu in *t*-BuOH was employed.
[c] The time required for complete conversion was judged from the hydrogen uptake curve.
[d] Conversion and enantioselectivity were determined by HPLC.

Table 4
Asymmetric reduction of ketone **2** with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**: scale-up

Entry	Scale (mmol)	S/C	Concd (M)[d]	Base[e]	Solvent ratio			*p* (bar)	*T* (°C)	*t* (h)	Yield,[f] ee[g] (%)
					2-PrOH	*t*-BuOH	H_2O				
1[a]	6.6	750:1	0.55	1.15 equiv KO^{t}Bu	26	63	11	25	68	23	87, 99.2
2[b]	68.4	1000:1	0.43	1.17 equiv KO^{t}Bu	6	84	10	80	65	22	93, 98.0
3[a]	11.0	3000:1	0.73	1.18 equiv KO^{t}Bu	3	87	10	25	65	67	91, >98
4[c]	5.0	5000:1	0.73	1.12 equiv KO^{t}Bu	7	83	10	25	75	<15	75, 97.0
5[c]	1.0	1000:1	0.5	3.0 equiv KOH	—	85	15	25	65	<12	55, n.d.

[a] The hydrogenation was performed in a 50 ml Parr autoclave.
[b] The hydrogenation was performed in a 100-ml Premex Hastelloy autoclave.
[c] The hydrogenation was performed in a Biotage Endeavour.
[d] The maximum concentration of 0.67 M is determined by the use of a 1 M solution of KO^{t}Bu in *t*-BuOH.
[e] A 1 M solution of KO^{t}Bu in *t*-BuOH or a 10 M aqueous solution of KOH was employed.
[f] Conversion by HPLC analysis was always >95%. Isolated yields after purification are reported (Table 5).
[g] The enantiomeric purity was determined by CE and/or HPLC.

cial allowing the reaction to reach almost complete conversion at a temperature of 60 °C. In addition, the use of lower temperature assured a small but significant increase in enantioselectivity that was consistently found to reach the value of 98% ee.

Next, we analysed the dependence of the reaction rates on the substrate concentration. It is known that asymmetric hydrogenations generally proceed more smoothly at higher concentrations.[37] In the experiments described in Tables 1 and 2, approximately 0.1 M solutions were employed, whereas the asymmetric reduction of the model substrate acetophenone can typically be performed in 1–1.5 M solution. A comparison of the results given in Tables 1–3 clearly indicates that an increase of the substrate concentration exerted a beneficial influence on the reaction rate. An increase in the substrate concentration is equivalent to increasing the base concentration and, when the catalyst loadings are reduced, the base to catalyst ratio, so the effect of these parameters cannot be judged in isolation. We think that both parameters (base concentration and base to catalyst ratio) are certain to have an effect on catalyst performance. In most cases, the presence of too little base accounts for the failure of the asymmetric hydrogenation. When solid potassium *tert*-butylate is employed, the base might not dissolve completely and the transformation might proceed sluggishly or not go to completion. In order to avoid these possible complications, solutions of potassium *tert*-butylate in *tert*-butanol were used. On the other hand, as already mentioned above, the presence of too much base seems to compromise the enantioselectivity of the transformation (entry 7).

It was eventually demonstrated (entries 3 and 12) that the presence of 2-propanol was not required and the reaction proceeded to full conversion, even in mixtures of *tert*-butanol (90%) and water (10%). One experiment was run under the new improved conditions (S/C 1500:1, 0.5 M) but without water (entry 10). The reaction was remarkably slower than in the presence of 10% of water and only produced 60% conversion and 48% ee. After 16 h under hydrogen at 65 °C, the reaction in the absence of water appeared as a dense gel. Conversely, a clear orange/yellow solution was always obtained in the presence of water (e.g., entry 9). The use of 10% of water as co-solvent seems to be optimum since reduced hydrogenation activity was observed in the presence of larger amounts of water (entry 6).

2.2. Upscale of the synthesis of diol 3 and removal of residual ruthenium

The asymmetric reduction of ketone **2** was conducted on a large scale applying the optimized reaction conditions and S/C ratios up to 5000:1. Full conversion of the starting material was always obtained (as judged by HPLC and/or ^{1}H NMR analysis) and isolated yields are reported in Table 4. Since potassium hydroxide is formed in an aqueous solution of potassium-*tert*-butylate in 2-propanol/*tert*-butanol, the direct use of potassium hydroxide as a base for the asymmetric hydrogenation of ketone **2** was also investigated Under the conditions described in entry 5 complete transformation occurred to alcohol **3**, although, under the conditions chosen, the isolated yield (55%) was somehow reduced.

Various methods for the purification of the crude product were investigated with the goal to isolate diol **3** virtually free from

Table 5
Asymmetric reduction of ketone **2** with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**: influence of the S/C ratio and the method of purification on the residual amount of ruthenium present in diol **3**

Entry from Table 4	S/C ratio	Ru, initial amount (ppm)	Method of purification	Ru, residual amount (ppm)
1	750:1	405	Chromatography CH_2Cl_2/MeOH	61
2	1000:1	270	Crystallization (acetone)	n.d.
3	3000:1	90	Crystallization (acetone/MTBE)	5
4	5000:1	55	Crystallization (acetone/MTBE)	3/10[a]
5	1000:1	270	Crystallization (acetone/MTBE)	21

[a] Crystallization afforded two crops of diol **3**.

Table 6
Removal of residual ruthenium from crude diol **3** by treatment with Smopex fibrous scavengers: initial ruthenium content: 270 ppm (calculated from a S/C ratio of 1000:1)

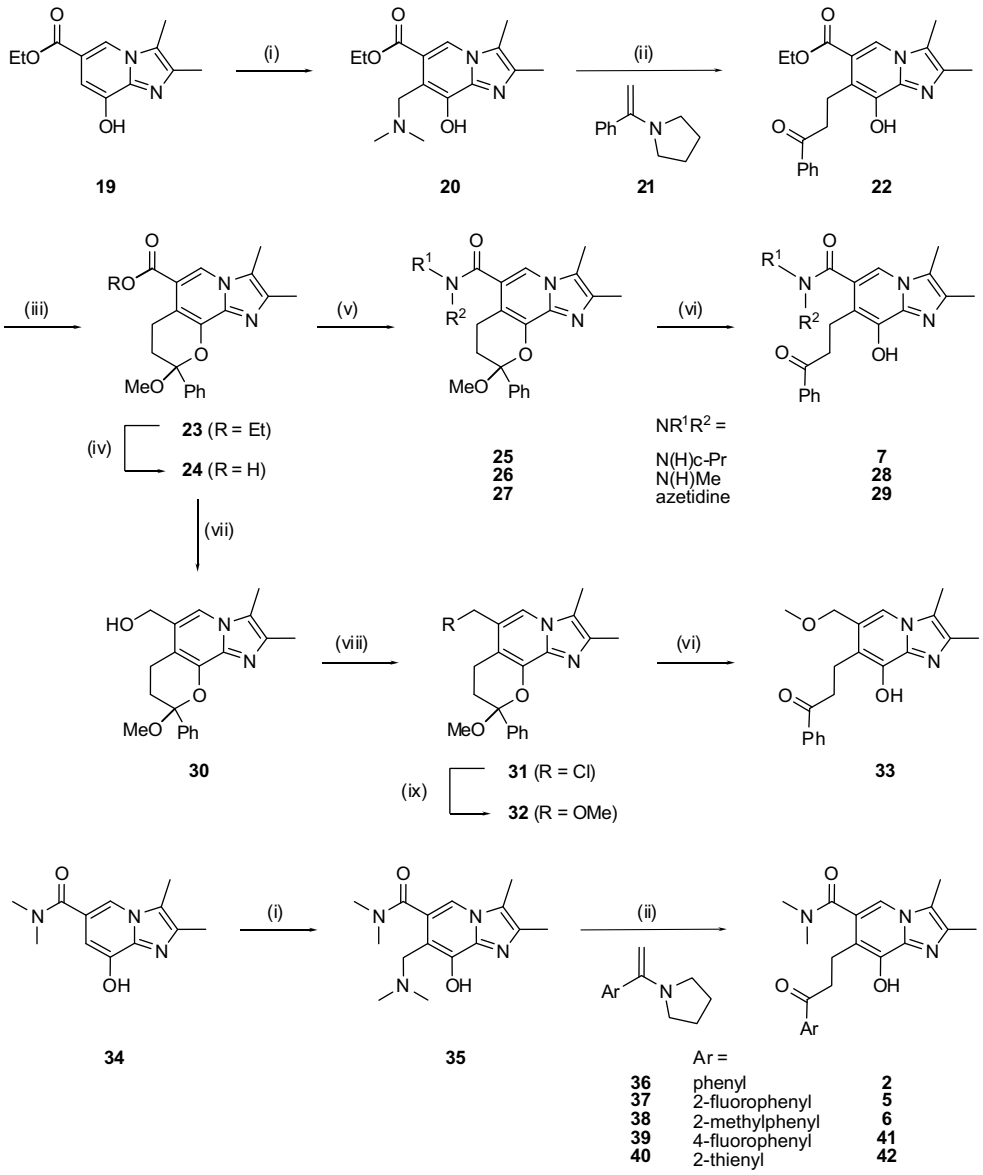
Entry	Procedure[a]	Smopex	Solvent	Residual Ru (ppm)
1	A	111	MeOH	170
2	A	112	MeOH	162
3	A	105	MeOH	182
4	A	110	MeOH	140
5	A	113	MeOH	187
6	A	103	MeOH	204
7	A	111	CH_2Cl_2	170
8	A	112	CH_2Cl_2	220
9	A	105	CH_2Cl_2	171
10	A	110	CH_2Cl_2	201
11	A	113	CH_2Cl_2	187
12	A	103	CH_2Cl_2	202
13	B	234	MeOH	195
14	B	202	MeOH	182
15	B	102	CH_2Cl_2	104
16	B	234	CH_2Cl_2	236
17	B	202	CH_2Cl_2	180
18	B	110	MeOH	179
19	B	103	MeOH	247

[a] Procedure A: A mixture of diol **3** (0.2 g) and Smopex (0.2 g) was heated in a Radley carousel in 10-ml solvent (45 °C, 20 h). Procedure B: A mixture of diol **3** (0.1 g) and Smopex (0.1 g) was shaken overnight in 5-ml solvent in a ChemSpeed multi-well reactor (45 °C, 20 h).

ruthenium residues (Table 5). According to a guideline published by the European Medicines Agency, a pharmaceutical substance should contain less than 10 ppm residual ruthenium.[38] Chromatographic purification was not ideal, since it did not remove all the ruthenium-containing species and caused an unnecessary drop in the overall yield (entry 1). Good results were achieved when the asymmetric hydrogenation was conducted at high S/C ratios and the crude alcohol **3** was crystallized from acetone or from a mixture of acetone with a co-solvent (e.g., MTBE) that reduces the solubility of diol **3** (entries 3–5).

The crude diol **3** obtained by asymmetric hydrogenation of ketone **2** with an S/C ratio of 1000:1 was used for Smopex screening (Table 6). Smopex fibrous scavengers are obtained by graft co-polymerization of polyolefin fibres using functionalised monomers. The metal-binding properties (chelating group) are added onto the exterior of the fibre.[39] In many cases, the open fibrous structure of the Smopex polymer accomplished excellent metal removal in short time. [40–42] All the samples of crude alcohol **3** treated with Smopex in methanol changed colour from brown to yellow, the samples treated with Smopex 103 and 110 in a matter of minutes. Three samples of alcohol **3** (entries 4, 9 and 17) were weighed and tested by ^{1}H NMR after the Smopex treatment and both purity and mass recovery (approximately 90% on small scale) were good. The results from ruthenium analysis showed that a maximum reduction of the ruthenium contents of about 50% was accomplished in the presence of Smopex 110. Presumably, the low performance of Smopex can be explained with the highly functional character of the heterocyclic substrate **3** endowing it with strong ruthenium-chelating properties. However, it should be pointed out that the screen was preliminary with the goal of identifying the most suitable Smopex fibres. It is likely that ruthenium recovery could be improved upon by optimization of the conditions.

Consequently, the preparation of ruthenium-free samples of diol **3** is best accomplished by the hydrogenation of ketone **2** at a high S/C ratio and subsequent purification of the crude product by crystallization. Furthermore, the use of hydrochloric acid to



Scheme 3. Reagents and conditions: (i) Eschenmoser's salt, CH_2Cl_2, rt, 10 min–2.5 h; (ii) 1-(1-arylvinyl)pyrrolidine **21** or **36**–**40**, K_2CO_3, DMF, 50 °C, 0.5–4 h [**2**, 49%; **5**, 51%; **6**, 54%; **22**, 55%; **41**, 46%; **42**, 45 %]; (iii) 2,2-dimethoxypropane, CH_2Cl_2, $MeSO_3H$, reflux, 6 h, 88%; (iv) KOH, MeOH, H_2O, 55 °C, 2 h, 97%; (v) (1) TBTU, CH_2Cl_2, reflux, 2 h; (2) amine, rt, 1–2 h [**25**, cyclopropylamine; **26**, methylamine (8 M solution in EtOH); **27**, azetidine]; (vi) HCl, THF, H_2O, 50–60 °C, 2–7 h (**7**, Σ78%; **28**, Σ73%; **29**, Σ 83%; **33**, 63%); (vii) $LiAlH_4$, THF, rt, 1 h, 86%; (viii) $SOCl_2$, CH_2Cl_2, 0 °C, 1 h, 99%; (ix) NaOMe, MeOH, 50 °C, 1.5 h, 98%.

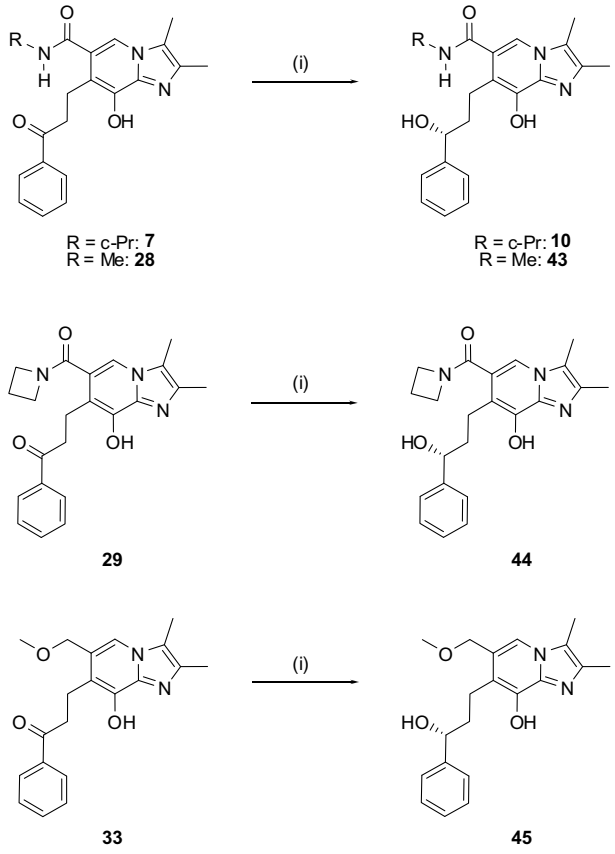
quench the reaction affording ruthenium species that can be removed more easily (e.g., by stirring of the alcohol **3** in organic solvents) is favourable.

2.3. Synthesis of analogues of the prochiral ketone 2

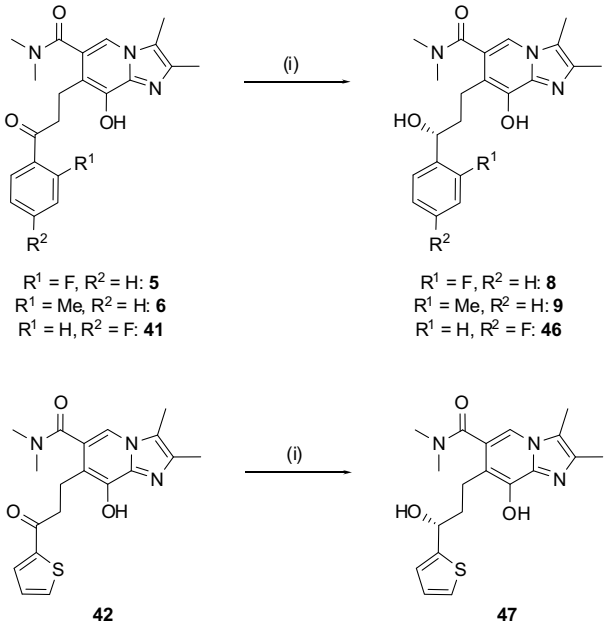
The preparation of prochiral ketones by alkylation of suitable imidazo[1,2-*a*]pyridine-building blocks (e.g., **19** and **34**) with Eschenmoser's salt and subsequent transformation of the resulting intermediates (e.g., **20** and **35**) with enamines (e.g., **21**, **36**–**40**) has previously been described and is illustrated in Scheme 3.[8] Ketone **22** was then transformed into the acetal **23**, which constitutes a versatile intermediate for the synthesis of other prochiral ketones. The prochiral ketones **7**, **28** and **29** bearing different carboxamide residues were obtained by hydrolysis of carboxylic ester **23**, amide coupling of the resulting carboxylic acid **24**, and cleavage of the acetal-protecting group present in intermediates **25**–**27**. Alternatively, the ester function of intermediate **23** was reduced with lithium aluminium hydride. The resulting alcohol **30** was activated by transformation with thionyl chloride and nucleophilic substitution was accomplished by treatment of chloride **31** with sodium methylate. Finally, ketone **33** bearing a methoxymethyl substituent was obtained by acid-catalyzed cleavage of acetal **32**. A variety of prochiral ketones containing different aryl substituents were prepared by the transformation of the Mannich base **35** with enamines **36**–**40**.

2.4. Extension of the methodology on structurally related prochiral ketones

We then applied the hydrogenation method developed for ketone **2** to the structurally related ketones **7**, **28**, **29** and **33** bearing different residues at the 6-position of the imidazo[1,2-*a*]pyridine scaffold (Scheme 4, Table 7). The solubility of the substrate and its anion is the main factor in determining the efficacy of the asymmetric hydrogenation. Substrates with NH amide functionality show very reduced solubility and therefore, the reductions of ketones **7** and **28**, containing a cyclopropyl carboxamide/methyl



Scheme 4. Reagents and conditions: (i) catalyst **18**, KO^{t}Bu, 2-PrOH, H_2O, 80 bar H_2, 65 °C, 16 h, see Table 7.



Scheme 5. Reagents and conditions: (i) catalyst **18**, KO^{t}Bu, 2-PrOH, H_2O, 80 bar H_2, 65 °C, 16 h, see Table 8.

Table 7
Asymmetric reduction of ketones **7**, **28**, **29** and **33** bearing different residues in 6-position of the imidazo[1,2-*a*]pyridine scaffold with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**

Entry	SM	Scale (mmol)	S/C	Concd (M)	KO^{t}Bu (equiv)[d]	Solvent ratio			*p* (bar)	*T* (°C)	*t* (h)	yield, ee[e] (%)
						2-PrOH	*t*-BuOH	H_2O				
1[a]	**7**	3.0	300:1	0.30	2.30	20	70	10	10	55–85	72	25, 98.4
2[b]	**28**	4.6	250:1	0.11	1.13	15	75	10	80	65	22	40, 98.4
3[b]	**29**	2.4	125:1[c]	0.06	1.17	10	80	10	80	65	46	51, 96.5
4[b]	**33**	3.3	250:1	0.09	1.48	5	84	11	80	65	23	84, 97.2

[a] The hydrogenation was performed in a 50-ml Parr autoclave.
[b] The hydrogenation was performed in a 100-ml Premex Hastelloy autoclave.
[c] The catalyst was added in two portions.
[d] A 1 M solution of KO^{t}Bu in *t*-BuOH was employed.
[e] The enantiomeric purity was determined by CE and/or HPLC.

carboxamide moiety, respectively, were performed with low S/C ratios (entries 1 and 2). Under these conditions, the hydrogenation of these derivatives proceeded smoothly achieving full conversion of the starting material; the rather low isolated yields reported in Table 7 are mainly due to problems encountered during the isolation of the sparingly soluble diols **10** and **43**.

Ketone **29** containing an azetidin-1-ylcarbonyl residue exhibited reduced reactivity and the reaction did not go to completion even after addition of a second portion of hydrogenation catalyst and an extended reaction period (Table 7, entry 3).[43] On the other hand, the enantiomeric purity of the corresponding alcohol **44** was not compromised (96.5% ee).

At an S/C ratio of 250:1, the reduction of ketone **33** possessing a methoxymethyl residue rather than a carboxamide residue proceeded to completion, even under dilute conditions, and afforded the corresponding alcohol **45** in 84% isolated yield and an enantiomeric purity of 97.2% ee.

Finally, we examined the asymmetric hydrogenation of a set of ketones **5**, **6**, **41** and **42**, which possess a substituted phenyl ring or a thiophene moiety (Scheme 5, Table 8). Isolated yields of the corresponding diols are reported in Table 8. As expected, ketone **6** containing an *ortho*-methylphenyl residue reacted more sluggishly than the parent compound **2** and complete conversion was only obtained after the addition of three portions of hydrogenation catalyst and an extended reaction period (entry 3).[43] Although high enantioselectivities and acceptable activities were obtained on small scale (reactions in Biotage Enveadour) with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18** in the presence of water (see Table 8, entry 2), it turned out that in multi-gram scale reactions, it was more beneficial to conduct the hydrogenation reaction in the absence of water (entries 4 and 5). With this improved procedure, the product **9** was isolated in good yield and excellent enantiomeric purity after crystallization from acetone. Once again, the beneficial effect of high substrate concentration is demonstrated in Table 8: In the presence of catalyst **18**, 74% conversion of ketone **6** was obtained at a S/C ratio of 200:1 and a substrate concentration of 0.25 M (entry 1). On the other hand, at a concentration of 0.5 M, quantitative transformation of ketone **6** was accomplished even at a S/C ratio of 250:1 (entry 2).

The reduction of ketones **5** and **41**, bearing a 2-fluorophenyl and a 4-fluorophenyl moiety, respectively, proceeded smoothly, even at high S/C ratios. Nevertheless, based on the hydrogen uptake curves, the hydrogenation of the *ortho*-fluoro substrate **5** proceeded more slowly than the reduction of the *para*-fluoro substrate **41**.[44] Alcohol **8** is much less soluble than its analogue **46** and upon cooling to room temperature at the end of the reaction, a large amount of product precipitated (entry 6). This suggested attempting the reactions at a higher temperature and with an increased amount of water (entries 7 and 8). Using 20% of water (entry 8) instead of 10%, however, produced a significant slowdown of the reaction.

Table 8
Asymmetric reduction of ketones **5**, **6**, **41** and **42** bearing different substituted phenyl and thiophene residues with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN]

Entry	SM	Scale (mmol)	S/C	Concd (M)	Base[d]	Solvent ratio			*p* (bar)	*T* (°C)	*t* (h)	yield, ee[i] (%)
						2-PrOH	*t*-BuOH	H_2O				
1[c]	**6**	0.5	200:1	0.25	1.20 equiv KO^{t}Bu	60	30	10	25	65	16	n.d.[j]
2[c]	**6**	1.0	250:1	0.50	1.20 equiv KO^{t}Bu	30	60	10	25	70	16	52, >95
3[a]	**6**	7.9	80:1[e]	0.21	2.15 equiv KO^{t}Bu	5	84	11	80	65	120	54, 92.2
4[b]	**6**	47.4	100:1	0.27	1.22 equiv KO^{t}Bu	67	33	—	80	70	96	97, 99.2
5[a]	**6**	15.8	250:1	0.27	1.20 equiv KO^{t}Bu	68	32	—	80	70	144	70, 98.6
6[c]	**5**	2.0	1000:1	0.50	1.20 equiv KO^{t}Bu	30	60	10	25	70	5	49[f], 95
7[c]	**5**	2.0	1000:1	0.50	1.20 equiv KO^{t}Bu	30	60	10	25	75	5	49[f], 98
8[c]	**5**	2.0	1000:1	0.50	1.20 equiv KO^{t}Bu	20	60	20	25	70	16	49[f], 98
9[c]	**5**	2.0	1000:1	0.50	1.20 equiv KO^{t}Bu	30	60	10	25	70	5	49[f], 84
10[c]	**5**	1.0	1000:1	0.50	2.0 equiv KOH	40	40	20	25	70	15	49[f], 94
11[c]	**41**	4.0	1000:1	0.67	1.10 equiv KO^{t}Bu	—	90	10	25	65	22[g]	74[h], 98
12[c]	**41**	4.0	2000:1	0.67	1.10 equiv KO^{t}Bu	—	90	10	25	65	22[g]	74[h], 98
13[a]	**42**	8.1	250:1	0.20	2.10 equiv KO^{t}Bu	10	80	10	80	65	23	63, 99.2

[a] The hydrogenation was performed in a 100-ml Premex Hastelloy autoclave.
[b] The hydrogenation was performed in a 300-ml Premex Hastelloy autoclave.
[c] The hydrogenation was performed in a Biotage Endeavour.
[d] A 1 M solution of KO^{t}Bu in *t*-BuOH or a 5 M aqueous KOH solution was used as base.
[e] The catalyst was added in three portions.
[f] In each case, >95% conversion took place. The samples from entries 6 to 10 were combined and purified affording 49% of diol **8** (94.6% ee).
[g] Actual reaction time according to hydrogen uptake curves: 10 h (entry 11), 17 h (entry 12).
[h] The samples from entries 11 to 12 were combined and purified affording 74% of diol **46** (>98% ee).
[i] The enantiomeric purity was determined by CE and/or HPLC.
[j] 74% conversion to diol **9**. The crude product was not purified.

Table 9
Conversion of chiral diols into 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines by Mitsunobu cyclization

Entry	Starting material	% ee (SM)	PPh_3 (equiv)	DIAD (equiv)	Solvent	Time (min)	Product	% ee (product)	Yield
1	**3**	99.2	1.5	1.5	THF	23	**1**	98.3	66
2	**8**	94.6	2.0	2.0	CH_2Cl_2	10	**52**	95.0	48
3	**9**	99.2	1.8	1.8	CH_2Cl_2	15	**53**	99.3[a]	56
4	**10**	98.4	2.0	2.0	CH_2Cl_2	20	**48**	98.2	50
5	**44**	96.5	2.0	2.0	CH_2Cl_2	15	**50**	96.8	48
6	**45**	97.2	2.0	2.0	CH_2Cl_2	10	**51**	98.6	62
7	**46**	98.6	2.0	2.0	THF	45	**54**	98.4	60
8	**47**	99.2	2.0	2.0	CH_2Cl_2	65	**55**	84.0	22

[a] The purity of compound **53** was increased by crystallization in the presence of fumaric acid.

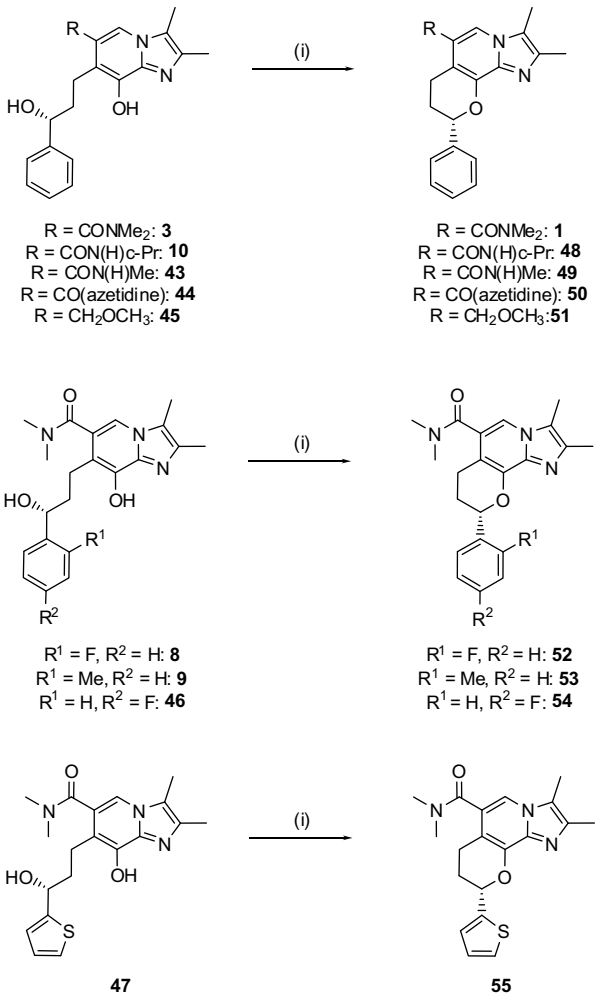
The use of potassium hydroxide was tested in a mixture of 2-propanol and *tert*-butanol and the reaction seemed to proceed to high conversion, although more slowly than under the standard conditions with potassium *tert*-butylate as a base (entry 10). The combination and purification of the crude products obtained from the reactions described in entries 6 to 10 afforded alcohol **8** in 49% yield and 94.6% ee. In the same manner, ketone **41** was transformed at S/C ratios of 1000:1 and 2000:1 (entries 11 and 12). Combination and purification of the corresponding crude products furnished alcohol **46** in 74% yield and >98% enantiomeric excess.

The versatility of the described hydrogenation method could be demonstrated by the asymmetric reduction of ketone **42**, which possesses a thiophene moiety. Under the reaction conditions given in Table 8, entry 13, the heterocyclic alcohol **47** was isolated in 63% yield and 99.2% ee.

In conclusion, small structural changes of the prochiral ketone employed for the hydrogenation reaction can account for big changes in solubility and reactivity.

2.5. Conversion of chiral diols into 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines with gastroprotective properties

The transformation of the chiral diols **3**, **8**–**10** and **43**–**47** into tricyclic 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines was accomplished by a Mitsunobu reaction, as described previously.[8,9,35] The results are summarized in Table 9 (see Scheme 6).



Scheme 6. Reagents and conditions: (i) PPh_3, DIAD, THF or CH_2Cl_2, rt, see Table 9.

The data presented in Table 9 clearly demonstrates that with the exception of thienyl derivative **55** (entry 8), the stereochemical information was conserved during the Mitsunobu cyclization. Presumably, in analogy to examples given in the literature, the reaction proceeded with complete inversion of the stereogenic center.[45,46] The biological and pharmacological evaluation of the target compounds with respect to their activity as potassium-competitive acid blocker has been published previously.[8,9]

3. Conclusion

The complex $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] **18**, which has not been reported previously, has been identified as a highly active and enantioselective catalyst for the asymmetric reduction of prochiral ketones possessing an imidazo[1,2-*a*]pyridine scaffold. Furthermore, catalyst **18** was found to be effective for the reduction of a variety of ketones for which unsatisfactory results were obtained in the presence of other Noyori catalysts, including $RuCl_2$[(*S*)-Xyl-BINAP][(*S*)-DAIPEN] **11** and $RuCl_2$[(*S*)-BINAP][(*S*)-DAIPEN] **4**. Whereas the reduction with other catalysts of the Noyori type has never been reported to occur under aqueous conditions, in the present case, the use of aqueous isopropanol or *tert*-butanol was not only tolerated but also turned out to be beneficial, especially when the reduction was conducted at high S/C ratios. Due to the outstanding performance of catalyst **18**, the asymmetric reduction of heterocyclic ketones was established as a key step in the synthesis of enantiopure tricyclic potassium-competitive acid blockers possessing a 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridine scaffold, like, for example, BYK 311319 (**1**).

4. Experimental

4.1. General

All chemicals in highest purity grade were purchased from the major chemical suppliers and were used without any further purification. The synthesis of the prochiral ketones **2**, **5**, **6**, **28**, **41** and **42** (substrates for the asymmetric hydrogenation experiments) and of carboxylic acid **24** (key intermediate for the synthesis of prochiral ketones) had been described previously.[8] The progress of the reaction was monitored on Macherey-Nagel HPTLC plates Nano-SIL 20 UV_{254} (0.20 mm layer, nano Silica Gel 60 with fluorescence indicator UV_{254}) using dichloromethane/methanol as solvent system. Column chromatography was performed with Merck Silica Gel 60 (70–230 mesh ASTM) with the solvent mixtures specified in the corresponding experiment. Spots were visualized either by iodine vapour or by irradiation with ultraviolet light (254 nm). Melting points (mp) were taken in open capillaries on a Büchi B-540 melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded with a Bruker DRX 200 FT-NMR spectrometer at a frequency of 200.1 MHz or a Bruker AV 400 FT-NMR spectrometer at a frequency of 400.1 MHz. $CDCl_3$ or DMSO-d_6 were used as solvents. Chemical shifts are reported as parts per million (δ ppm) with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra were obtained on a Bruker Daltonics MicroTOF Focus instrument using electrospray ionization (ESI positive). Elemental analysis was performed on a Carlo Erba 1106 C, H, N analyzer. The enantiomeric purity of the chiral intermediates and target compounds was determined by capillary electrophoresis (CE) and/or high pressure liquid chromatography (HPLC). The experimental conditions for the separation of the enantiomers by HPLC are given for each example in Section 4. The separation by CE was performed using one of the following experimental setups: instrument: Agilent CE-3D; capillary: Agilent bubble cell 64.5 cm × 50 μm (Method A), Agilent barefused silica bubble

48.5 cm × 50 μm (Method B); buffer: 50 mM sodium phosphate, pH 2.5 (Agilent); chiral selector: 40 mM heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (Cyclolab); voltage: 30 kV; temperature: 10 °C (method A), 20 °C (method B). The number of the method employed for the corresponding analysis is given in parentheses in Section 4. All of the HPLC columns used for preparative and analytical purposes are commercially available: CHIRALPAK® AD-H (DAICEL Chemical Industries Ltd, Tokyo or Chiral Technologies-Europe SARL, Ilkirch, France); Lichrochart® 240 ChiraDex® (Merck KgaA, Darmstadt, Germany); XTerra RP 18 (Waters Corporate, Milford, Massachusetts, USA). For selected compounds prepared by asymmetric catalytic hydrogenation, the ruthenium content was determined by applying the following analytical method: 100 mg of sample was weighed into a Zirconium crucible and ashed at 600 °C in a muffle furnace to remove all carbonaceous materials. The resultant residue was then fused with 2 g of >95% pure sodium peroxide over a Mekker burner and allowed to cool. The melt was leached with 10ml of analaR-grade concentrated (37%) hydrochloric acid and warmed on a hotplate for about 30 min to remove excess peroxide. The solution was cooled to ambient temperature before making up to 100 ml with 18 Megaohm deionised water in a previously acid-soaked volumetric flask. This was then allowed to equilibrate in a water bath until it reached a constant temperature of 20 °C. The ruthenium analysis was performed with by an Elan 6100 ICP-MS run in standard mode using a 20-fold dilution of the above solution. Rhodium (50 ppb) was employed throughout the experiment as an internal standard in all reagent blanks, standards and analytical samples.

4.2. (9*S*)-2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 1

In a flame-dried flask filled with argon, diol **3** (1.20 g, 3.3 mmol, 99.2% ee) was suspended in dry THF (15 ml). After the addition of triphenylphosphine (1.30 g, 5.0 mmol) and the dropwise addition of DIAD over a period of 8 min (0.99 g, 4.9 mmol), a dark-green solution was obtained, which was stirred for 15 min at room temperature. A colourless precipitate was formed, which was isolated by filtration, washed with THF (6 ml) and diethyl ether (8 ml), and dried in vacuo. The title compound was isolated in 66% yield (97.6–98.3% ee): mp 252–254 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 4.0 min/0.8 area-%, RT [(9*S*)-enantiomer] = 4.4 min/99.1 area-%, 98.4% ee; determination of the enantiomeric excess by CE (method A): MT [(9*S*)-enantiomer] = 19.5 min/98.8 area-%; MT [(9*R*)-enantiomer] = 20.3 min/1.2 area-%; 97.6% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.14 (m_c, 1H), 2.26 (s, m_c, 4H), 2.35 (s, 3H), 2.47 (m_c), 2.78, 2.87 (m_c, s, 4H), 3.01 (s, 3H), 5.26 (dd, 1H), 7.42 (m_c, 5H), 7.79 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{24}N_3O_2$ $[M+H]^+$ calcd: 350.1863. Found: 350.1847. Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.62; H, 6.72; N, 11.69.

4.3. (3*R*)-8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 3

4.3.1. Asymmetric catalytic hydrogenation with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18, screen of reaction conditions

Samples of ketone **2** (cf. Tables 1–3) and catalyst **18** were weighed in glass liners that were then placed in a Biotage Endeavour (eight-well pressure parallel reactor, overhead stirrers and heating block). The vessel was sealed and the wells purged by pressurising five times with nitrogen to 2 bar and releasing the pressure. The base (1 M solution of potassium *tert*-butylate in *tert*-butanol or aqueous solution of potassium hydroxide) and the solvent were then injected. The wells were purged by pressurising five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to the set temperature and pressurised to the set pressure of hydrogen. After the period specified in the table (the reaction time was judged from the hydrogen uptake curve) the hydrogen pressure was released and the reaction mixtures were transferred to round-bottomed flasks with the help of methanol (10 ml). The solvent was evaporated and the crude samples were analysed by HPLC (determination of conversion and enantiomeric excess, cf. above). In some cases, the conversion determined by HPLC was compared with the conversion determined by ^{1}H NMR. With both methods, almost identical values were obtained.

4.3.2. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 (S/C = 750:1), purification by column chromatography

Ketone **2** (2.40 g, 6.6 mmol) and catalyst **18** (11 mg, 8.8 μmol, S/C = 750:1) were weighed in a glass liner and placed in a hydrogenation vessel that was sealed and flushed with nitrogen. A solution of potassium *tert*-butylate in *tert*-butanol (1 M, 7.60 ml, 7.6 mmol), water (1.3 ml) and isopropanol (3.2 ml) were added and the reaction solution was degassed by pressurising to 20 bar hydrogen and releasing the pressure five times. The reaction was placed in an oil bath set at 68 °C (the internal temperature was estimated to be 63–65 °C) and stirred under 25 bar hydrogen for 23 h. The hydrogen uptake ceased after 6–7 h. The solvent was evaporated and the yellow solid residue (full conversion and >98% ee by HPLC) was dissolved in dichloromethane (100 ml). A saturated solution of ammonium chloride was added (100 ml) and 2 N hydrochloric acid was added dropwise to reach neutral pH. The organic layer was separated and dried over sodium sulfate, filtered and evaporated to give a brown solid residue (2.5 g, >98% ee by HPLC) that was purified by column chromatography [silica gel, eluant: dichloromethane/methanol = 9.1 (v/v), then 4:1 (v/v)]. Upon evaporation of the solvent, a pale green solid (2.1 g, 87% yield) was isolated; the pure title compound as confirmed by ^{1}H NMR spectroscopy and CE (99.2% ee): mp 136 °C; residual Ru: 61 ppm; determination of the enantiomeric excess by HPLC (column: Merck Lichrocart 240 Chiradex; mobile phase: methanol/water = 2:8 (v/v) [35 min], 7:3 (v/v) [5 min], 2:8 (v/v) [5 min]; flow rate: 1 ml/min; room temperature; detection at 210 nm): RT [(3*S*)-enantiomer] = 13.5 min, RT [(3*R*)-enantiomer] = 15.5 min; determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 17.7 min/0.4 area-%, MT [(3*R*)-enantiomer] = 18.0 min/99.6 area-%; 99.2% ee.

4.3.3. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 (S/C = 1000:1), purification by crystallization from acetone

In a flask filled with argon, ketone **2** (25.00 g, 68.4 mmol) was suspended in *tert*-butanol (55 ml) and water (15 ml). Potassium *tert*-butylate (80.0 ml of a 1 M solution in *tert*-butanol, 80 mmol) was slowly added. The yellow suspension was stirred for 20 min at room temperature, diluted with isopropanol (10 ml), and gently heated. A brown solution was obtained, which was treated with catalyst **18** (85 mg, 68 μmol, S/C = 1000:1) and stirred for 10 min. Under inert conditions, the reaction mixture was transferred into a 300-ml autoclave, purged with hydrogen (3×), subjected to a hydrogen pressure of 80 bar, and heated to 65 °C for 22 h. The mixture was cooled to room temperature and the hydrogen pressure was released. The yellow solution was poured on a mixture of saturated ammonium chloride solution (300 ml) and

dichloromethane (600 ml), neutralized by addition of 6-M hydrochloric acid, and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 40 ml). The combined organic phases were washed with water (100 ml), dried over sodium sulfate, and concentrated under reduced pressure. A yellow foamy solid (30 g) remained, which was dried in vacuo and dissolved in warm acetone (200 ml). Upon cooling to room temperature, a slurry was obtained, which was stirred for 2 h at room temperature. The precipitate was isolated by filtration, washed with acetone (30 ml) and diethyl ether (80 ml), and dried in vacuo. The title compound was obtained in 93% yield (23.2 g of a colourless solid, enantiomeric excess: 98.0% ee): mp 185–186 °C; determination of the enantiomeric excess enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 14.5 min/1.0 area-%; MT [(3*R*)-enantiomer] = 14.7 min/98.1 area-%; 98.0% ee.

4.3.4. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 (S/C = 3000:1), purification by crystallization from acetone/MTBE

Ketone **2** (4.02 g, 11.0 mmol) and the catalyst **18** (4.5 mg, 4 μmol, S/C = 3000:1) were weighed in a glass vial which was placed in a 50-ml Parr hydrogenation reactor with a magnetic stirrer. The reactor was purged with nitrogen and the solvents and base were added via the injection port: 13 ml of a 1 M solution of potassium *tert*-butylate in *tert*-butanol, water (1.5 ml), and isopropanol (0.5 ml). The reactor was purged with hydrogen by pressurising to 10 bar and releasing the pressure several times, then it was placed in an oil bath heated at 90 °C. The internal temperature was maintained between 55 and 65 °C and the hydrogen pressure was maintained at 25 bar. The reaction was left under stirring for 67 h. The crude product was analysed by HPLC (conversion: 97.5%, >98% ee). The dense reaction mixture was diluted to 70 ml by adding isopropanol. Concentrated hydrochloric acid was added dropwise until reaching a pH value of 7. Inorganic salts were precipitated and then removed by filtration through Celite. The Celite pad was washed with more isopropanol (30 ml) and the solvent was evaporated to give 4.2 g of crude title compound. The crude material was taken up in acetone (20 ml) and methyl *tert*-butyl ether (40 ml), heated and allowed to cool. The product was collected as an off-white solid and dried under vacuum (3.7 g, 91% yield, >98% ee). mp 223–225 °C; residual Ru: 5 ppm; determination of the enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 17.6 min/1.3 area-%; MT [(3*R*)-enantiomer] = 17.8 min/95.9 area-%; 97.4% ee.

4.3.5. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 (S/C = 5000:1), purification by crystallization from acetone/MTBE

Samples of ketone **2** (1.83 g, 5.0 mmol) and catalyst **18** (1.2 mg, 1 μmol, S/C = 5000:1) were weighed in a glass liner that was then placed in a Biotage Endeavour. The vessel was sealed and the well purged by pressurising five times with nitrogen to 2 bar and releasing the pressure. Potassium *tert*-butylate (5.60 ml of a 1 M solution in *tert*-butanol, 5.6 mmol) and the solvent (0.5 ml of 2-propanol and 0.7 ml of water) were then injected. The wells were purged by pressurising five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to 75 °C and a hydrogen pressure of 25 bar was applied. After 15 h (the reaction time was judged from the hydrogen uptake curve) the hydrogen pressure was released and the reaction mixture diluted to 40 ml by addition of 2-propanol. Concentrated hydrochloric acid was added to reach pH 7 (measured on wet pH paper). The salts were filtered off, the residue on the filter was washed with more 2-propanol (40 ml) and the solvent was evaporated. The solid residue was taken up in acetone (10 ml) and MTBE (10 ml) and the resulting off-white solid was collected (0.82 g, 45% yield). The mother liquor was evaporated and then taken up in acetone (5 ml) and MTBE (25 ml). The resulting off-white solid was collected and dried (0.55 g, 30% yield): residual Ru: 3 ppm (batch 1)/10 ppm (batch 2); determination of the enantiomeric excess by HPLC (column: Merck Lichrocart 240 Chiradex; mobile phase: methanol/water = 2:8 (v/v) [35 min], 7:3 (v/v) [5 min], 2:8 (v/v) [5 min]; flow rate: 1 ml/min; room temperature; detection at 210 nm): RT [(3*S*)-enantiomer] = 13.5 min, RT [(3*R*)-enantiomer] = 15.5 min, 97% ee.

4.3.6. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 (S/C = 1000:1) in the presence of KOH, purification by crystallization from acetone/MTBE

Samples of ketone **2** (0.36 g, 1.0 mmol) and catalyst **18** (1.2 mg, 1 μmol, S/C = 1000:1) were weighed in a glass liner that was then placed in a Biotage Endeavour. The vessel was sealed and the well purged by pressurising five times with nitrogen to 2 bar and releasing the pressure. Potassium hydroxide (0.30 ml of a 10 M aqueous solution, 3.0 mmol) and *tert*-butanol were then injected. The wells were purged by pressurising five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to 65 °C and a hydrogen pressure of 25 bar was applied. After 12 h (the reaction time was judged from the hydrogen uptake curve) the hydrogen pressure was released. The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (10 ml). A saturated solution of ammonium chloride (10 ml) was added and 2 M hydrochloric acid was added to reach pH 7. The organic layer was separated, washed with more ammonium chloride solution, dried over sodium sulfate and evaporated to give 0.25 g of an off-white solid (68% mass recovery). The material was slurried in acetone (1 ml) and MTBE (10 ml) and the resulting white solid was collected and dried (0.2 g, 55% yield): residual Ru: 21 ppm.

4.3.7. Smopex screening

Procedure A: Samples of 0.2 g of alcohol **3** were dissolved in methanol or dichloromethane (10 ml) and Smopex (0.2 g) was added. The reactions were heated overnight in a Radley carousel (magnetic stirring) and filtered to remove the resin. The solvent was evaporated and the residual amount of ruthenium determined. Procedure B: Samples of 0.1 g of alcohol **3** were dissolved in dichloromethane or methanol (5 ml) and Smopex (0.1 g) was added. The reactions were shaken overnight in a ChemSpeed multi-well reactor, filtered, and the solvent evaporated. A mixture of dichloromethane (1 ml) and MTBE (1 ml) was added and the solvent evaporated again. The residual amount of ruthenium present in the solid residues was determined. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.81 (m_c, 2H), 2.30, 2.33 (2s, 6H), 2.50 (br m_c), 2.78, 2.91 (2s, 6H), 4.49 (t, 1H), 5.69 (br s), 7.25 (m_c, 5H), 7.59 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{26}N_3O_3$ $[M+H]^+$ calcd: 368.1969. Found: 368.1961.

4.4. 8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-*a*]pyridine-6-carboxylic acid cyclopropylamide 7

A suspension of acetal **25** (1.55 g, 4.0 mmol) in THF (30 ml) was treated with 2 M hydrochloric acid (10 ml). Gradually, a yellow solution was obtained which was heated to 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (30 ml), 2 M sodium hydroxide solution was added to the stirred solution until a neutral pH value was obtained, and stirring was continued for 2 h at room temperature. Formation of a precipitate occurred, which was isolated by filtration, washed with water (10 ml) and dried in vacuo (50 °C, 17 h). The pure title compound (1.3 g, 78% overall yield) was iso-

lated in the form of a colourless solid: mp 279–281 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 0.55 (m_c, 2H), 0.67 (m_c, 2H), 2.34 (s, 3H), 2.40 (s, 3H), 2.80 (m_c, 1H), 3.05 (t, 2H), 3.27 (t, 2H), 6.43 (br s, 1H), 7.57 (m_c, 3H), 7.89 (s, 1H), 7.98 (m_c, 2H), 8.54 (d, 1H); HRMS (ESI) m/z $C_{22}H_{24}N_3O_3$ $[M+H]^+$ calcd: 378.1812. Found: 378.180. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.17; H, 6.16; N, 10.96.

4.5. (3*R*)-7-[3-(2-Fluorophenyl)-3-hydroxy-propyl]-8-hydroxy-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 8

Five samples of ketone **5** (total amount: 3.46 g, 9.0 mmol) and catalyst **18** (each reaction was conducted with S/C 1000:1, total amount: 11 mg, 9 μmol) were weighed in glass liners that were then placed in a Biotage Endeavour. The vessel was sealed and the wells purged by pressurising five times with nitrogen to 2 bar and releasing the pressure. The base (1 M solution of potassium *tert*-butylate in *tert*-butanol or 5 M aqueous solution of potassium hydroxide, cf. Table 10) and the solvent (cf. Table 10) were then injected. The wells were purged by pressurising five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to 70–75 °C and pressurised to 25 bar hydrogen. After 5–16 h, the hydrogen pressure was released and the reaction mixtures were transferred to round bottomed flasks with the help of methanol (10 ml). The solvent was evaporated and the crude samples were analysed by ^{1}H NMR (>95% conversion) and HPLC.

The samples were then combined and the solvent evaporated. The resulting solid was taken up in dichloromethane and saturated ammonium chloride solution. Hydrochloric acid (2 M) was added to reach neutral pH. The organic layer was separated, dried over sodium sulfate, and evaporated. A solid residue (2.76 g) was isolated. Half of the sample was purified by column chromatography [silica gel, eluant: dichloromethane/methanol = 9:1 (v/v)]. The title compound (0.79 g) was isolated as a pale green solid. The other half of the crude product was suspended in methyl *tert*-butyl ether. The suspension was heated, allowed to cool to room temperature, and filtered. The title compound (1.21 g) was obtained as a pale yellow solid. The two samples were combined and purified further by trituration with methyl *tert*-butyl ether to yield alcohol **8** (1.70 g of a pale yellow solid, 49% yield, 94.6% ee): mp 234–236 °C; determination of the enantiomeric excess by HPLC (column: Merck Lichrocart 240 Chiradex; mobile phase: methanol/water = 17:83 (v/v); flow rate: 1 ml/min; room temperature; detection at 210 nm): RT [(3*S*)-enantiomer] = 20.1 min, RT [(3*R*)-enantiomer] = 22.4 min; determination of the enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 18.0 min/2.7 area-%; MT [(3*R*)-enantiomer] = 18.3 min/96.6 area-%; 94.6% ee; ^{1}H NMR (DMSO-d_6 + 1 drop of MeOD, 200 MHz): δ = 1.80 (m_c, 2H), 2.31, 2.33 (2s, 6H), 2.55 (m_c), 2.79, 2.91 (2s, 6H), 4.82 (t, 1H), 7.17 (m_c, 3H), 7.51 (dt, 1H), 7.59 (s, 1H); HRMS (ESI) m/z $C_{21}H_{25}FN_3O_3$ $[M+H]^+$ calcd: 386.1874. Found: 386.1877.

4.6. (3*R*)-8-Hydroxy-7-[3-hydroxy-3-(2-methylphenyl)-propyl]-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 9

4.6.1. Asymmetric catalytic hydrogenation with $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 in the presence of water

In a flask filled with argon, ketone **6** (3.00 g, 7.9 mmol) was suspended in *tert*-butanol (15 ml). Water (4 ml) and potassium *tert*-butylate (17.0 ml of a 1 M solution in *tert*-butanol, 17 mmol) were added and the yellow suspension was stirred for 15 min at room temperature. After addition of isopropanol (2 ml) a clear solution was obtained. The hydrogenation catalyst **18** (39 mg, 31 μmol, S/C = 250:1) was added and stirring was continued for 10 min. Under inert conditions, the solution was transferred into a 100-ml autoclave, purged with hydrogen (3×) and a hydrogen pressure of 80 bar was applied. The reaction mixture was heated to 65 °C for 23 h, cooled to room temperature (^{1}H NMR: 33% turnover) and more hydrogenation catalyst **18** (40 mg, 31 μmol) was added. The hydrogenation was continued for 3 days (80 bar, 65 °C). The autoclave was cooled to room temperature (^{1}H NMR: 79% turnover), another portion of hydrogenation catalyst (40 mg, 31 μmol) added, and the reaction was continued for another 23 h (80 bar, 65 °C). The reaction mixture was cooled to room temperature (dark-brown solution) and poured on a stirred mixture of saturated ammonium chloride solution (50 ml) and dichloromethane (120 ml). A pH value of 7 was adjusted by the addition of 2 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with water (20 ml), dried over sodium sulfate, and evaporated to dryness. The dark-brown residue [^{1}H NMR: mixture of starting material (10%) and title compound (90%)] was purified by column chromatography [80 g of silica gel, eluant: dichloromethane/methanol = 100:2 (v/v)]. Concentration of the corresponding fractions afforded pure samples of the starting material (210 mg, 7% yield) and of the title compound (2.10 g, 70% yield). A suspension of the title compound (2.10 g) in isopropyl acetate (20 ml) was heated to 50 °C and allowed to cool to room temperature. Stirring was continued for 2 h at room temperature. The precipitate was isolated by filtration, washed with isopropyl acetate (5 ml) and dried in vacuo. A slightly green solid (1.8 g, 54% yield) was isolated, which was characterized as a mixture of the title compound (90 wt %, 92.2% ee) and isopropyl acetate (10 wt %): determination of the enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 15.2 min/3.9 area-%; MT [(3*R*)-enantiomer] = 15.7 min/95.2 area-%; 92.2% ee.

4.6.2. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 in the absence of water (S/C = 100:1)

In a flask filled with argon, ketone **6** (18.00 g, 47.4 mmol) was suspended in dry isopropanol (120 ml), which had been degassed with argon. Potassium *tert*-butylate (58.0 ml of a 1 M solution in *tert*-butanol, 58 mmol) was added and a yellow solution was obtained. The hydrogenation catalyst **18** (590 mg, 0.47 mmol,

Table 10
Experimental details for the reduction of ketone **5**

Starting material	Base	Solvent	Conditions
0.77 g (2.0 mmol)	*t*-BuOK (2.40 ml, 2.4 mmol)	*i*-PrOH (1.2 ml), H_2O (0.4 ml)	70 °C, 5 h
0.77 g (2.0 mmol)	*t*-BuOK (2.40 ml, 2.4 mmol)	*i*-PrOH (1.2 ml), H_2O (0.4 ml)	75 °C, 5 h
0.77 g (2.0 mmol)	*t*-BuOK (2.40 ml, 2.4 mmol)	*i*-PrOH (0.8 ml), H_2O (0.8 ml)	70 °C, 16 h
0.77 g (2.0 mmol)	*t*-BuOK (2.40 ml, 2.4 mmol)	*i*-PrOH (1.2 ml), H_2O (0.4 ml)	70 °C, 5 h
0.38 g (1.0 mmol)	KOH (0.40 ml, 2.0 mmol)	*i*-PrOH (0.8 ml), *t*-BuOH (0.8 ml)	70 °C, 15 h

S/C = 100:1) was added and stirring was continued for several minutes. Under inert conditions, the solution was transferred into a 300-ml autoclave, purged with hydrogen (3×) and a hydrogen pressure of 80 bar was applied. The reaction mixture was heated to 70 °C for 4 days, cooled to room temperature and poured on a stirred mixture of saturated ammonium chloride solution (250 ml) and dichloromethane (400 ml). The phases were separated and the aqueous phase extracted with dichloromethane (2 × 50 ml). The combined organic phases were washed with water (2 × 80 ml), dried over sodium sulfate and evaporated to dryness. The yellow foamy residue (22 g) was dissolved in hot acetone (85 ml). Upon cooling, crystallization occurred. The slurry was stirred for 17 h at room temperature and for 2 h at 0 °C. The precipitate was isolated by filtration, washed with acetone (15 ml) and diethyl ether (30 ml) and dried in vacuo. The title compound was isolated in the form of a colourless solid (17.5 g, 97% yield,: 99.2% ee), which contained 10 wt % of acetone and 4 wt % of water: determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 18.1 min/0.4 area-%; MT [(3*R*)-enantiomer] = 18.5 min/98.3 area-%; 99.2% ee.

4.6.3. Asymmetric catalytic hydrogenation with $RuCl_2$ [(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18 in the absence of water (S/C = 250:1)

In a flask filled with argon, ketone **6** (6.00 g, 15.8 mmol) was suspended in dry isopropanol (40 ml), which had been degassed with argon. Potassium *tert*-butylate (19.0 ml of a 1 M solution in *tert*-butanol, 19 mmol) was added and a yellow solution was obtained. The hydrogenation catalyst **18** (80 mg, 64.3 μmol, S/C = 250:1) was added and stirring was continued for several minutes. Under inert conditions, the solution was transferred into a 100-ml autoclave, purged with hydrogen (3×) and a hydrogen pressure of 80 bar was applied. The reaction mixture was heated to 70 °C for 1 day, cooled to room temperature and examined by TLC-analysis (presence of starting material). The hydrogenation was continued for 5 days (80 bar, 70 °C). The autoclave was cooled to room temperature and the reaction mixture was poured on a stirred mixture of saturated ammonium chloride solution (120 ml) and dichloromethane (150 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 30 ml). The combined organic phases were washed with water (2 × 30 ml), dried over sodium sulfate and evaporated to dryness. The yellow foamy residue (4.9 g) was dissolved in hot acetone (30 ml). Upon cooling, crystallization occurred. The slurry was stirred for 17 h at room temperature and for 2 h at 0 °C. The precipitate was isolated by filtration, washed with acetone (5 ml) and diethyl ether (10 ml) and dried in vacuo. The alcohol **9** was isolated in the form of a grey solid (4.2 g, 70% yield, 98.6% ee): determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 19.0 min/0.7 area-%; MT [(3*R*)-enantiomer] = 19.5 min/96.7 area-%; 98.6% ee (A). ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.73 (m_c, 2H), 2.23, 2.31, 2.33 (3 s, 9H), 2.50 (m_c), 2.70, 2.79 (m_c, s, 4H), 2.93 (s, 3H), 4.71 (t, 1H), 5.56 (br s), 7.14 (m_c, 3H), 7.41 (d, 1H), 7.60 (s, 1H), isopropyl acetate: 1.17 (d), 1.96 (s), 4.86 (septet); HRMS (ESI) *m*/*z* $C_{22}H_{28}N_3O_3$ $[M+H]^+$ calcd: 382.2125. Found: 382.2114.

4.7. (3*R*)-8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid cyclopropylamide 10

Ketone **7** (1.13 g, 3.0 mmol) and catalyst **18** (12.4 mg, 10 μmol, S/C = 300:1) were weighed in a glass vial that was placed in a 50 ml Parr hydrogenation reactor with a magnetic stirrer. The reactor was purged with nitrogen and the solvents and base were added via the injection port: 7.0 ml of a 1 M solution of potassium *tert*-butylate in *tert*-butanol, water (1 ml) and isopropanol (2 ml). The reactor was purged with hydrogen by pressurising to 10 bar and releasing the pressure several times, after which it was placed in an oil bath heated at 90 °C. The internal temperature was maintained between 55 and 85 °C and the hydrogen pressure maintained at 10 bar. The reaction was left under stirring for 3 days. The crude product was analyzed by HPLC (conversion: >95%, >95% ee). The reaction mixture was evaporated to give a pale yellow solid. This was suspended in methanol (100 ml) and a saturated solution of ammonium chloride (100 ml) and concentrated hydrochloric acid was added to obtain pH 7. The resulting pale green cloudy solution was evaporated. Dichloromethane (150 ml) and water (150 ml) were added and the resulting suspension was allowed to filter overnight to yield an off-white solid that was dried under vacuum (~1 g) and further purified by column chromatography [silica gel, eluant: dichloromethane/methanol = 1:1 (v/v)]. Upon evaporation of the corresponding fractions, 0.94 g of a colourless solid was obtained, which consisted of the title compound in the form of its hydrochloride salt and ammonium chloride (as indicated by ^{1}H NMR spectroscopy and elemental analysis). In order to remove the inorganic salts, the sample was dissolved in saturated sodium bicarbonate solution (5 ml), water (10 ml) and methanol (50 ml). The suspension was heated at reflux, at which point the solid dissolved almost completely. The obtained green solution was filtered and a pH value of 8 was adjusted by addition of saturated ammonium chloride solution (2 ml). After evaporation of the methanol, a white suspension was formed which was stirred for 30 min at room temperature. The solid was isolated by filtration, washed with water (10 ml), methanol (5 ml), and acetone (10 ml), and dried in vacuo (55 °C, 6 h). This furnished the pure title compound (280 mg of a grey solid, 25% yield, 98.4% ee): mp 283–285 °C; determination of the enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 20.01 min/0.77 area-%; MT [(3*R*)-enantiomer] = 20.49 min/94.20 area-%; 98.4% ee; ^{1}H NMR (DMSO-d_6 + traces of MeOH, 200 MHz): δ = 0.53 (m_c, 2H), 0.69 (m_c, 2H), 1.79 (m_c, 2H), 2.30, 2.35 (2s, 6H), 2.72 (m_c, 3H), 4.47 (t, 1H), 5.26 (br s), 7.26 (m_c, 5H), 7.68 (s), 8.39 (d, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{26}N_3O_3$ $[M+H]^+$ calcd: 380.1969. Found: 380.1962.

4.8. $RuCl_2$[(*S*)-Xyl-P-Phos][(*S*)-DAIPEN] 18

4.8.1. Small-scale preparation

(Benzene)dichlororuthenium dimer (CAS 37366-09-9, 1 equiv) and (*S*)-Xyl-P-Phos (CAS 443347-10-2, commercially available from Strem Chemicals and Alfa Aesar, 1.03 equiv) were placed in a Schlenk flask that was evacuated and filled with argon. Anhydrous, degassed DMF (2 ml per mmol) was added and the flask was placed in an oil bath pre-heated to 105 °C. The reaction was stirred at 105 °C for 1.5 h. (*S*)-DAIPEN (CAS 148369-91-9, commercially available from Strem Chemicals, 1.1 equiv) was added and the reaction was stirred at room temperature for 3 h. At this stage, a sample of the reaction mixture was diluted in chloroform-D+ and analysed by ^{31}P NMR spectroscopy. Only the two doublets of the desired complex and the small excess of free ligand were visible. The DMF was evaporated under vacuum (heating necessary) and the residue was dissolved in anhydrous degassed dichloromethane (5–10 ml per mmol) and placed on top of a silica gel column in a Schlenk filter under argon. The product was eluted with dichloromethane/methyl *tert*-butyl ether = 1:1 (v/v). The clear yellow solution was collected in a Schlenk flask and the solvent was evaporated to give a yellow/green solid that was further dried under vacuum overnight. The isolated yield was 90% (adaptation of a general procedure described by Noyori et al.[27] in). The complexes **4**, **11** and **17** can be prepared in an analogous manner.

4.8.2. Preparation up to 30 g scale

(Benzene)dichlororuthenium dimer (CAS 37366-09-9, 1 equiv) and (*S*)-Xyl-P-Phos (CAS 443347-10-2, commercially available from Strem Chemicals and Alfa Aesar, 1.02 equiv) were placed in a flask under inert atmosphere (nitrogen). Anhydrous, degassed DMF (~1 ml per mmol) and toluene (2 ml per mmol) were added, and the reaction mixture was heated to 105 °C (external temperature) and stirred for 2 h. The brown suspension became a red solution. (*S*)-DAIPEN (CAS 148369-91-9, commercially available from Strem Chemicals, 1.04 equiv) was added as a solid or as a DMF/toluene solution (0.5 ml per mmol). The reaction mixture was stirred at 105 °C for 1–2 h, then allowed to cool to 70 °C. The reaction mixture became a yellow solution. The solvent was evaporated under high vacuum while the reaction mixture was kept at 70 °C. Toluene (2 ml per mmol) was added and removed again under reduced pressure. The procedure was repeated until a powder was obtained. 2-Propanol (2.5 ml per mmol) was added to the solid residue and the mixture was heated at reflux until a clear dark solution was obtained. The reaction mixture was allowed to cool to room temperature and then further stirred at 0 °C (ice bath) for 30 min. The resulting yellow solid was collected and cold 2-propanol was used to rinse the flask and wash the cake. The solid was allowed to dry in the air before it was dried under vacuum overnight (60–78% isolated yield of **18** on the first crop). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = −0.01 (d, 3H, –CH–CH_3), 0.67 (d, 3H, –CH–CH_3), 1.86 (br m$_c$, 1H, CH), 2.14 (s, 6H, ArCH_3), 2.24 (s, 6H, ArCH_3), 2.27 (s, 6H, ArCH_3), 2.37 (s, 6H, ArCH_3), 2.40 (br d, 1H, NH), 2.99 (br t, 1H, CH), 3.46 (s, 3H, Ar-OCH_3), 3.65 (s, 3H, Ar-OCH_3), 3.87 (s, 3H, Py-OCH_3), 3.88 (s, 3H, Py-OCH_3), 3.95 (s, 6H, Py-OCH_3), 4.10 (br d, 1H, NH), 4.42 (br d, 1H, NH), 4.68 (br d, 1H, NH), 6.42 (d, 1H, Ar-H), 6.90 (m$_c$, 8H, Ar-H), 7.10 (m$_c$, 3H, Ar-H), 7.36 (m$_c$, 2H, Ar-H), 7.50–7.65 (m, 8H, Ar-H). ^{31}P NMR ($CDCl_3$, 400 MHz): 46.0 (distorted dd).

4.9. 9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid cyclopropylamide 25

In a flask filled with argon, a suspension of carboxylic acid **24** (1.55 g, 4.4 mmol) in dry dichloromethane (30 ml) was treated with TBTU (1.55 g, 4.8 mmol). The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. After the addition of cyclopropylamine (0.28 g, 0.34 ml, 4.9 mmol) a yellow solution was obtained, and it was stirred for 1.5 h at room temperature. The reaction mixture was poured on a mixture of ice water (20 ml), saturated sodium bicarbonate solution (10 ml), and dichloromethane (10 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with water (20 ml), extracted with 2 M sodium hydroxide solution (10 ml), washed with another portion of water (20 ml) and dried over sodium sulfate. Evaporation of the solvent afforded the title compound (1.6 g of a colourless solid, 85% yield): mp 297–299 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 0.58 (m$_c$, 2H), 0.71 (m$_c$, 2H), 1.87 (m$_c$, 1H), 2.31, 2.36, 2.40 (s, m$_c$, s, 7H), 2.73 (m$_c$), 3.0 (m$_c$, s, 4H), 7.48 (m$_c$, 3H), 7.62 (m$_c$, 2H), 7.94 (s, 1H), 8.45 (d, 1H); HRMS (ESI) *m*/*z* $C_{23}H_{26}N_3O_3$ $[M+H]^+$ calcd: 392.1969. Found: 392.1960. Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.53; H, 6.47; N, 10.74.

4.10. (9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridin-6-yl)-azetidin-1-yl methanone 27

In a flask filled with argon, a suspension of carboxylic acid **24** (2.20 g, 6.2 mmol) in dry dichloromethane (40 ml) was treated with TBTU (2.20 g, 6.9 mmol). The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. After the addition of azetidine (0.38 g, 0.45 ml, 6.7 mmol) a yellow-brown solution was obtained, and it was stirred for 2 h at room temperature. The reaction mixture was poured on ice water (40 ml) and dichloromethane (20 ml). The stirred biphasic mixture was neutralized (pH 8) by addition of 2 M sodium hydroxide solution. Stirring was continued for several min and the phases were separated. The organic phase was washed with water (20 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue (3.6 g of a red oil) was purified by column chromatography [80 g of silica gel, eluant: dichloromethane, then dichloromethane/methanol = 20:1 (v/v)]. A colourless solid (2.5 g, 89% yield) was isolated, which was a mixture of the title compound (87 wt %) and tetramethyl urea (13 wt %) [as judged from the ^{1}H NMR spectrum]: ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.90 (m$_c$, 1H), 2.27, 2.32, 2.39 (m$_c$, 2 s, 9H), 2.61 (m$_c$), 2.69 (tetramethyl urea), 2.95, 3.00 (m$_c$, s, 4H), 4.05 (m$_c$, 4H), 7.47 (m$_c$, 3H), 7.62 (m$_c$, 2H), 7.94 (s, 1H); HRMS (ESI) *m*/*z* $C_{23}H_{26}N_3O_3$ $[M+H]^+$ calcd: 392.1969. Found: 392.1958.

4.11. (8-Hydroxy-2,3-dimethyl-7-(3-oxo-3-phenyl-propyl)-imidazo[1,2-*a*]pyridin-6-yl)-azetidin-1-yl methanone 29

A suspension of crude acetal **27** (2.40 g) in THF (100 ml) was treated with 2 M hydrochloric acid (15 ml). Gradually, a clear solution was obtained which was heated to 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (80 ml) and 2 M sodium hydroxide solution was added to the stirred solution until a neutral pH value was obtained. Stirring was continued for 2 h at room temperature and a further 2 h at 0 °C. Formation of a precipitate then occurred, which was isolated by filtration, washed with water (50 ml) and isopropanol (20 ml) and dried in vacuo (60 °C, 17 h). The pure title compound (1.95 g, 83% overall yield) was isolated in the form of a colourless solid: mp 279–281 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.21 (m$_c$, 2H), 2.32 (s, 3H), 2.37 (s, 3H), 2.98 (t, 2H), 3.26 (t, 2H), 4.03 (m$_c$, 4H), 5.68 (br s), 7.59 (m$_c$, 3H), 7.77 (s, 1H), 7.99 (m$_c$, 2H); HRMS (ESI) *m*/*z* $C_{22}H_{24}N_3O_3$ $[M+H]^+$ calcd: 378.1812. Found: 378.1814.

4.12. (9-Methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridin-6-yl)-methanol 30

In a flame-dried flask filled with argon, carboxylic ester **23** (3.80 g, 10.0 mmol) was suspended in dry THF (70 ml). At room temperature, lithium aluminium hydride (1.0 g, 26 mmol) was added in small portions over a period of 30 min. Stirring was continued for 30 min at room temperature and the reaction mixture was poured slowly on a mixture of saturated ammonium chloride solution (30 ml) and dichloromethane (150 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (4 × 15 ml). The combined organic phases were washed with water (2 × 20 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue, 2.9 g of a yellow solid, was dried in vacuo and characterized as the pure title compound (86% yield): mp 257–258 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.91 (m$_c$, 1H), 2.31, 2.35, 2.37 (s, m$_c$, s, 7H), 2.70 (m$_c$, 1H), 2.86 (m$_c$, 1H), 2.98 (s, 3H), 4.53 (s, 2H), 5.19 (br s, 1H), 7.48 (m$_c$, 3H), 7.63 (m$_c$, 2H), 7.75 (s, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{23}N_2O_3$ $[M+H]^+$ calcd: 339.1703. Found: 339.1695.

4.13. 6-Chloromethyl-9-methoxy-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*] pyridine 31

A suspension of alcohol **30** (2.20 g, 6.5 mmol) in dry dichloromethane (80 ml) was cooled to 0 °C and thionyl chloride (0.59 ml, 0.96 g, 8.1 mmol) was added slowly. A yellow solution was obtained which was stirred for 1 h at 0 °C and then poured on saturated sodium bicarbonate solution (20 ml). The biphasic

mixture was stirred until gas evolution had ceased and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 10 ml). The combined organic phases were washed with saturated ammonium chloride solution (20 ml) and water (30 ml), dried over sodium sulfate and the solvent was evaporated under reduced pressure. A colourless, foamy solid was isolated which was dried in vacuo. The title compound (2.3 g, 99% yield) was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.93 (m_c, 1H), 2.31, 2.38, 2.41 (2s, m_c, 7H), 2.82 (m_c, 1H), 2.99, 3.02 (s, m_c, 4H), 4.89 (dd, 2H), 7.47 (m_c, 3H), 7.63 (m_c, 2H), 8.10 (s, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{22}ClN_2O_2$ $[M+H]^+$ calcd: 357.1364. Found: 357.1351.

4.14. 9-Methoxy-6-methoxymethyl-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine 32

The crude 6-chloromethyl-derivative **31** (2.20 g, 6.2 mmol) was dissolved in dry methanol (20 ml). After addition of sodium methylate (solution: 30 wt % in methanol, 3.0 ml, 17 mmol) a yellow suspension was obtained which was heated to 50 °C. Within a period of 90 min a yellow solution was formed which was concentrated to a volume of 10 ml and poured on a mixture of saturated ammonium chloride solution (15 ml) and dichloromethane (20 ml). A pH-value of 7 was adjusted by the addition of 2 M hydrochloric acid and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 8 ml). The combined organic phases were washed with water (20 ml), dried over sodium sulfate and concentrated under reduced pressure. An oily residue was isolated which was dried in vacuo. The title compound (2.1 g of a foamy solid, 98% yield) was used for the next step without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.92 (m_c, 1H), 2.30, 2.37, 2.37 (2s, m_c, 7H), 2.70 (m_c, 1H), 2.90 (m_c, 1H), 2.98 (s, 3H), 3.33 (s), 4.43 (s, 2H), 7.46 (m_c, 3H), 7.62 (m_c, 2H), 7.82 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{25}N_2O_3$ $[M+H]^+$ calcd: 353.1860. Found: 353.1852.

4.15. 3-(8-Hydroxy-6-methoxymethyl-2,3-dimethyl-imidazo[1,2-*a*]pyridin-7-yl)-1-phenyl-propan-1-one 33

A solution of the crude acetal **32** (2.00 g, 5.7 mmol) in THF (40 ml) was treated with 2 M hydrochloric acid (15 ml). The yellow solution was stirred at room temperature for 19 h, heated to 50 °C for 2 h and poured on a mixture of water (50 ml) and dichloromethane (100 ml). A neutral pH-value was adjusted by addition of 2 M sodium hydroxide solution and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 15 ml). The combined organic phases were washed with water (30 ml), dried over sodium sulfate and evaporated to dryness. The solid residue (1.9 g) was suspended in acetone (2 ml). After a period of 30 min, the precipitate was isolated by filtration, washed with cold acetone (2 ml) and diethyl ether (10 ml) and dried in vacuo. The pure title compound was isolated in 63% yield (1.20 g of a slightly yellow solid): mp 167–168 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.30, 2.35 (2s, 6H), 2.97 (t, 2H), 3.25, 3.28 (m_c, s, 5H), 4.47 (s, 2H), 7.11 (br s), 7.58 (m_c, 3H), 7.71 (s, 1H), 7.98 (m_c, 2H); HRMS (ESI) *m*/*z* $C_{20}H_{23}N_2O_3$ $[M+H]^+$ calcd: 339.1703. Found: 339.1695.

4.16. (3*R*)-8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid methylamide 43

In a flask filled with argon, ketone **28** (1.60 g, 4.6 mmol) was suspended in *tert*-butanol (26 ml) and water (4 ml). Potassium *tert*-butylate (5.20 ml of a 1 M solution in *tert*-butanol, 5.2 mmol) was slowly added. The yellow suspension was diluted with isopropanol (5 ml) and gently heated. The hydrogenation catalyst **18** (23 mg, 18 μmol, S/C = 250:1) was added to the warm mixture and stirring was continued for 5 min. Under inert conditions, the suspension was transferred into a 100-ml autoclave and the flask was washed with isopropanol (3 ml). The reactor was purged with hydrogen (3×), subjected to a hydrogen pressure of 80 bar and heated to 65 °C for 22 h. The mixture was cooled to room temperature and the hydrogen pressure was released. The thick suspension was poured on a mixture of saturated ammonium chloride solution (40 ml) and dichloromethane (180 ml) and a neutral pH value was adjusted by the addition of 2 M hydrochloric acid. The biphasic mixture was stirred for 30 min. The phases were separated and the aqueous phase was extracted with dichloromethane (4 × 15 ml). The combined organic phases were concentrated in vacuo and coevaporated in the presence of dichloromethane (3×). In order to remove inorganic salts, the residue (3.3 g) was dissolved at 50 °C in a mixture of water (150 ml), dichloromethane (350 ml), methanol (70 ml) and chloroform (150 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (4 × 30 ml). The combined organic phases were washed with water (40 ml), dried over sodium sulfate and concentrated under reduced pressure. A colourless solid (0.93 g) remained which was crystallized from methanol (55 ml). After a period of 17 h, the precipitate was isolated by filtration, washed with methanol (2 ml) and diethyl ether (8 ml) and dried in vacuo. Alcohol **43** was obtained in 40% yield (0.65 g of a colourless solid, 98.4% ee): mp 250–252 °C; determination of the enantiomeric excess by CE (method B): MT [(3*S*)-enantiomer] = 18.0 min/0.8 area-%; MT [(3*R*)-enantiomer] = 18.4 min/99.2 area-%; 98.4% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.81 (m_c, 2H), 2.30, 2.35 (2s, 6H), 2.72, 2.73 (m_c, d, 5H), 4.47 (t, 1H), 5.66 (br s), 7.33 (m_c, 5H), 7.71 (s, 1H), 8.26 (bq, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{24}N_3O_3$ $[M+H]^+$ calcd: 354.1812. Found: 354.1811.

4.17. (3*R*)-[8-Hydroxy-7-(3-hydroxy-3-phenyl-propyl)-2,3-dimethyl-imidazo[1,2-*a*]pyridin-6-yl]-azetidin-1-yl methanone 44

In a flask filled with argon, ketone **29** (0.90 g, 2.4 mmol) was suspended in *tert*-butanol (28 ml) and water (4 ml). Potassium *tert*-butylate (2.75 ml of a 1 M solution in *tert*-butanol, 2.8 mmol) was slowly added. The yellow suspension was diluted with isopropanol (4 ml) and gently heated. The hydrogenation catalyst **18** (12 mg, 10 μmol, S/C = 250:1) was added to the warm mixture and stirring was continued for several minutes. Under inert conditions, the yellow solution was transferred into a 100-ml autoclave. The reactor was purged with hydrogen (3×) subjected to a hydrogen pressure of 80 bar and heated to 65 °C for 22 h. The reaction mixture was cooled to room temperature and the hydrogen pressure was released. The crude product was analysed by ^{1}H NMR spectroscopy (50% conversion). More hydrogenation catalyst (12 mg, 10 μmol) was added and the hydrogenation was continued for 24 h (80 bar, 65 °C). After cooling to room temperature and release of the hydrogen pressure, the solution was poured on a mixture of saturated ammonium chloride solution (40 ml) and dichloromethane (120 ml) and a neutral pH value was adjusted by the addition of 2 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with water (20 ml), dried over sodium sulfate and concentrated in vacuo. The residue was analysed by ^{1}H NMR spectroscopy (40% of starting material, 60% of title compound) and purified by column chromatography [40 g of silica gel, eluant: dichloromethane/methanol = 100:3 (v/v)]. After evaporation of the corresponding fractions, 280 mg (31%) of starting material was recovered. The title compound was isolated in the form of a slightly green solid (550 mg, 61% yield), which was further purified by treatment with

acetone (8 ml). The resulting slurry was stirred for 30 min at room temperature. The precipitate was isolated by filtration and washed with acetone (2 ml) and diethyl ether (10 ml). The pure title compound was obtained in 35% yield (0.32 g of a beige solid, 51% corrected yield, 96.5% ee): mp 242–244 °C; determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 18.4 min/1.7 area-%; MT [(3*R*)-enantiomer] = 18.6 min/95.8 area-%; 96.5% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.82 (m_c, 2H), 2.17 (m_c, 2H), 2.30, 2.35 (2s, 6H), 2.66 (m_c, 2H), 3.95 (m_c, 4H), 4.50 (t, 1H), 5.18 (br s), 7.28 (m_c, 5H), 7.68 (s, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{25}N_3O_3$ $[M+H]^+$ calcd: 380.1969. Found: 380.1957.

4.18. (3*R*)-7-(3-Hydroxy-3-phenyl-propyl)-6-methoxymethyl-2,3-dimethyl-imidazo[1,2-*a*]pyridin-8-ol 45

In a flask filled with argon, ketone **33** (1.10 g, 3.3 mmol) was suspended in *tert*-butanol (26 ml) and water (4 ml). Potassium *tert*-butylate (4.90 ml of a 1 M solution in *tert*-butanol, 4.9 mmol) was added slowly. The yellow suspension was diluted with isopropanol (2 ml) and warmed gently (40 °C). A clear solution was obtained, which was treated with the hydrogenation catalyst **18** (16 mg, 13 μmol, S/C = 250:1) and stirring was continued for several minutes. Under inert conditions, the solution was transferred into a 100 ml autoclave, purged with hydrogen (3×) and a hydrogen pressure of 80 bar was applied. After a period of 23 h at 65 °C, the reaction mixture was cooled to room temperature and the hydrogen pressure was released. The yellow solution was poured on a mixture of saturated ammonium chloride solution (40 ml) and dichloromethane (120 ml). A pH value of 7 was adjusted by addition of 2 M hydrochloric acid and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 8 ml). The combined organic phases were washed with water (25 ml), dried over sodium sulfate and concentrated in vacuo. A green solid residue (1.05 g) remained which was treated with acetone (4 ml). The slurry was stirred for 30 min at 0 °C. The precipitate was isolated by filtration, washed with acetone (1 ml) and diethyl ether (5 ml) and dried in vacuo. The title compound (0.93 g of a colourless solid) was obtained in 84% yield (97.2% ee): mp 198–200 °C; determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 21.8 min/1.4 area-%; MT [(3*R*)-enantiomer] = 22.7 min/98.6 area-%; 97.2% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.81 (m_c, 2H), 2.29, 2.33 (2s, 6H), 2.68 (m_c, 2H), 3.21 (s, 3H), 4.31 (s, 2H), 4.56 (t, 1H), 5.23 (br s), 7.27 (m_c, 5H), 7.61 (s, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{25}N_2O_3$ $[M+H]^+$ calcd: 341.1860. Found: 341.1843.

4.19. (3*R*)-7-[3-(4-Fluorophenyl)-3-hydroxy-propyl]-8-hydroxy-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 46

Two samples of ketone **41** (1.54 g, 4.0 mmol each) and catalyst **18** (5 mg, 4 μmol for S/C 1000:1 and 2.5 mg, 2 μmol for S/C 2000:1) were weighed in glass liners that were then placed in a Biotage Endeavour (eight-well pressure parallel reactor, overhead stirrers and heating block). The vessel was sealed and the wells were purged by pressurising five times with nitrogen to 2 bar and releasing the pressure. The base (4.40 ml of a 1 M solution of potassium *tert*-butylate in *tert*-butanol, 4.4 mmol) and the solvent (0.6 ml of water and 1.0 ml of *tert*-butanol) were then injected. The wells were purged by pressurising five times with hydrogen to 25 bar (under stirring) and releasing the pressure. The reaction was then heated to 65 °C and pressurised to 25 bar hydrogen. The hydrogen uptake was monitored and the pressure was kept constant at 25 bar. After 22 h the hydrogen was released and the reaction mixtures (clear red solutions) were transferred to round-bottomed flasks with the help of methanol (10 ml). The solvent was evaporated and the crude samples were analysed by ^{1}H NMR (full conversion) and HPLC (>98% ee of (*R*)-enantiomer). The samples were then combined and dissolved in dichloromethane (100 ml). Aqueous saturated ammonium chloride solution (100 ml) was added and the pH changed to neutral by the addition of 2 M hydrochloric acid. The organic layer was separated, dried over sodium sulfate and evaporated to give 3.03 g of the crude title compound (97% mass recovery). The crude material was purified by chromatography [silica gel, eluant: dichloromethane/methanol = 95:5, 9:1, 8:2 (v/v)]. The title compound was co-eluted with a green compound. The corresponding fractions were combined and evaporated (2.3 g, 74% yield, >98% ee): mp 115–117 °C; determination of the enantiomeric excess by HPLC (column: Merck Lichrocart 240 Chiradex; mobile phase: methanol/water = 2:8 (v/v); flow rate: 1 ml/min; room temperature; detection at 210 nm): RT [(3*S*)-enantiomer] = 11.9 min (0.6 area-%), RT [(3*R*)-enantiomer] = 14.1 min (99.4 area-%), 98.8% ee; determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 18.9 min/0.7 area-%; MT [(3*R*)-enantiomer] = 19.1 min/98.7 area-%; 98.6% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.80 (m_c, 2H), 2.30, 2.33 (2s, 6H), 2.43 (m_c), 2.79, 2.91 (2s, 6H), 4.51 (t, 1H), 4.93 (br s), 7.13 (t, 2H), 7.33 (dd, 2H), 7.59 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{25}FN_3O_3$ $[M+H]^+$ calcd: 386.1874. Found: 386.1860.

4.20. (3*R*)-8-Hydroxy-7-[3-hydroxy-3-thiophen-2-yl-propyl]-2,3-dimethyl-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 47

In a flask filled with argon, ketone **42** (3.00 g, 8.1 mmol) was suspended in *tert*-butanol (15 ml). Water (4 ml) and potassium *tert*-butylate (17.0 ml of a 1 M solution in *tert*-butanol, 17 mmol) was added and the yellow suspension was warmed gently (40 °C). After the addition of isopropanol (4 ml), a clear solution was obtained within a period of 10 min. The hydrogenation catalyst **18** (40 mg, 32 μmol, S/C = 250:1) was added and stirring was continued for 5 min at 40 °C. Under inert conditions, the warm solution was transferred into a 100 ml autoclave, purged with hydrogen (3×), and a hydrogen pressure of 80 bar was applied. After a period of 23 h at 65 °C, the reaction mixture was cooled to room temperature and the hydrogen pressure was released. The dark yellow solution was poured on a mixture of saturated ammonium chloride solution (50 ml) and dichloromethane (130 ml). A pH value of 7 was adjusted by the addition of 2 M hydrochloric acid and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 15 ml). The combined organic phases were washed with water (20 ml), dried over sodium sulfate and concentrated in vacuo. A dark-brown solid residue (3.2 g) remained, which was treated with acetone (12 ml). The slurry was stirred for 1 h. The precipitate was isolated by filtration, washed with acetone (3 ml) and diethyl ether (8 ml) and dried in vacuo. The title compound (1.9 g of a colourless solid) was obtained in 63% yield (99.2% ee): mp 158–160 °C; determination of the enantiomeric excess by CE (method A): MT [(3*S*)-enantiomer] = 17.4 min/0.4 area-%; MT [(3*R*)-enantiomer] = 17.7 min/99.2 area-%; 99.2% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.85 (m_c, 2H), 2.31, 2.33 (2s, 6H), 2.55 (m_c), 2.81, 2.96 (2s, 6H), 4.74 (t, 1H), 4.96 (br s), 6.95 (m_c, 2H), 7.37 (dd, 1H), 7.60 (s, 1H); HRMS (ESI) *m*/*z* $C_{19}H_{24}N_3O_3S$ $[M+H]^+$ calcd: 374.1533. Found: 374.1523.

4.21. (9*S*)-2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid cyclopropylamide 48

In a flame-dried flask filled with argon, diol **10** (1.30 g, 3.4 mmol, 98.4% ee) was suspended in dry dichloromethane (50 ml). After the addition of triphenylphosphine (1.80 g,

6.9 mmol) and the dropwise addition of DIAD (1.40 g, 6.9 mmol) a red-brown suspension was obtained which was stirred for 20 min at room temperature. The thin suspension was filtrated [recovery of starting material (70 mg, 5% yield)]. The filtrate was concentrated under reduced pressure to a volume of 15 ml and loaded on a column packed with 50 g of silica gel. The title compound was eluted with dichloromethane/methanol [100:3 (v/v)]. Evaporation of the corresponding fractions afforded a solid residue (850 mg), which was crystallized from hot acetone (8 ml). A suspension was formed which was stirred for 1 h at room temperature. The title compound was isolated by filtration, washed with acetone (2 ml) and diethyl ether (5 ml) and dried in vacuo (610 mg of a colourless solid, 50% yield, 98.2% ee): mp 280–282 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 3.3 min/0.9 area-%, RT [(9*S*)-enantiomer] = 3.5 min/99.1 area-%, 98.2% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 0.58 (m_c, 2H), 0.71 (m_c, 2H), 2.02 (m_c, 1H), 2.26 (s, m_c, 4H), 2.37 (s, 3H), 2.66–3.08 (m, 3H), 5.23 (dd, 1H), 7.42 (m_c, 5H), 7.86 (s, 1H), 8.42 (d, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{24}N_3O_2$ $[M+H]^+$ calcd: 362.1863. Found: 362.1852.

4.22. (9*S*)-(2,3-Dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridin-6-yl)-azetidin-1-yl methanone 50

In a flame-dried flask filled with argon, diol **44** (280 mg, 0.77 mmol, 96.5% ee) was suspended in dry dichloromethane (15 ml). After the addition of triphenylphosphine (0.39 g, 1.5 mmol) and the dropwise addition of DIAD (0.31 g, 1.5 mmol) a brown solution was obtained which was stirred for 15 min at room temperature. The reaction mixture was concentrated under reduced pressure to a volume of 5 ml and loaded on a column packed with 20 g of silica gel. The title compound was eluted with dichloromethane/methanol [100:1 (v/v), then 20:1 (v/v)]. Evaporation of the corresponding fractions afforded the pure title compound, which was dried in vacuo (130 mg of a colourless solid, 48% yield, 96.8% ee): mp 256–258 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 4.1 min/1.6 area-%, RT [(9*S*)-enantiomer] = 4.6 min/98.1 area-%, 96.8% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.20, 2.25 (m_c, s, 7H), 2.37 (s, 3H), 2.67 (m_c, 1H), 2.90 (m_c, 1H), 4.04 (m_c, 4H), 5.25 (dd, 1H), 7.43 (m_c, 5H), 7.87 (s, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{24}N_3O_2$ $[M+H]^+$ calcd: 362.1863. Found: 362.1860.

4.23. (9*S*)-6-Methoxymethyl-2,3-dimethyl-9-phenyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine 51

In a flame-dried flask filled with argon, diol **45** (0.90 g, 2.6 mmol, 97.2% ee) was suspended in dry dichloromethane (12 ml). After the addition of triphenylphosphine (1.40 g, 5.3 mmol) and the dropwise addition of DIAD (1.07 g, 5.3 mmol), a green solution was obtained which was stirred for 10 min at room temperature. The reaction mixture was concentrated under reduced pressure to a volume of 6 ml and loaded on a column packed with silica gel (25 g). The by-products were eluted with dichloromethane/methanol = 100:1 (v/v) and the polarity of the eluant was increased to 100:2 (v/v). Evaporation of the corresponding fractions furnished a yellow oil (1.1 g), which was dissolved in diethyl ether (15 ml). After a period of 4 days, a precipitate had formed, which was isolated by filtration, washed with diethyl ether (5 ml) and dried in vacuo. The title compound was isolated in 62% yield (0.52 g of a colourless solid, 98.6% ee): mp 146–148 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: isopropanol/*n*-hexane = 1:9 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 237 nm): RT [(9*R*)-enantiomer] = 12.9 min/0.7 area-%, RT [(9*S*)-enantiomer] = 19.3 min/99.3 area-%, 98.6% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.15, 2.25, 2.35 (m_c, 2s, 8H), 2.83 (m_c, 2H), 3.30 (s), 4.42 (s, 2H), 5.20 (dd, 1H), 7.43 (m_c, 5H), 7.76 (s, 1H); HRMS (ESI) *m*/*z* $C_{20}H_{23}N_2O_2$ $[M+H]^+$ calcd: 323.1754. Found: 323.1736. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.67; H, 6.77; N, 7.73.

4.24. (9*S*)-9-(2-Fluorophenyl)-2,3-dimethyl-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 52

In a flame-dried flask filled with argon, diol **8** (1.00 g, 2.6 mmol, 94.6% ee) was suspended in dry dichloromethane (20 ml). After the addition of triphenylphosphine (1.40 g, 5.3 mmol) and the dropwise addition of DIAD (1.10 g, 5.4 mmol) a brown solution was obtained which was stirred for 10 min at room temperature. The reaction solution was concentrated under reduced pressure to a volume of 8 ml and loaded on a column packed with 30 g of silica gel. The title compound was eluted with dichloromethane/methanol 100:1 (v/v). Evaporation of the corresponding fractions furnished a yellow foamy solid (1 g), which was dissolved in hot acetone (3 ml). Upon cooling to room temperature a suspension was obtained, which was stirred for 1 h at room temperature and for 1 h at 0 °C. The precipitate was removed by filtration, washed with cold acetone (1 ml) and diethyl ether (5 ml) and dried in vacuo. The title compound was isolated in 48% yield (0.46 g of a colourless solid, 95.0% ee): mp 190–192 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 3.84 min/2.5 area-%, RT [(9*S*)-enantiomer] = 4.30 min/97.5 area-%, 95.0% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.18, 2.25 (m_c, s, 5H), 2.35 (s, 3H), 2.55 (m_c), 2.83, 2.90 (m_c, s, 4H), 3.02 (s, 3H), 5.48 (dd, 1H), 7.29 (m_c, 2H), 7.43 (m_c, 1H), 7.54 (m_c, 1H), 7.81 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{23}FN_3O_2$ $[M+H]^+$ calcd: 368.1769. Found: 368.1752. Anal. Calcd for $C_{21}H_{22}FN_3O_2$: C, 68.65; H, 6.04; N, 11.44. Found: C, 68.46; H, 6.05; N, 11.28.

4.25. (9*S*)-2,3-Dimethyl-9-(2-methylphenyl)-7*H*-8,9-dihydro-pyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 53

In a flame-dried flask filled with argon, diol **9** (17.30 g, 45.3 mmol, containing 14 wt % of solvent, 99.2% ee) was suspended in dry dichloromethane (220 ml). After the addition of triphenylphosphine (21.00 g, 80.1 mmol) and the dropwise addition of DIAD (16.50 g, 81.6 mmol) over a period of 10 min, a dark-green solution was obtained which was stirred for 5 min at room temperature. The reaction solution was concentrated under reduced pressure and loaded on a column packed with 300 g of silica gel. The title compound was eluted with ethyl acetate/methanol [100:3 (v/v)]. Evaporation of the corresponding fractions furnished a foamy, slightly green solid (11.8 g), which was treated with a solution of fumaric acid (6.7 g, 57.8 mmol) in hot acetone (350 ml). The resulting green solution was stirred for 30 min at 50 °C, at which point crystallization occurred. Stirring was continued for 17 h at room temperature and for 30 min at 0 °C. The salt of the title compound with fumaric acid was isolated by filtration, washed with acetone (10 ml) and diethyl ether (20 ml) and dried in vacuo (14.5 g of a colourless solid, molar ratio of title compound to fumaric acid = 1:2, 54% yield, 65% corrected yield): mp 205–206 °C; ^{1}H

NMR (DMSO-d_6, 200 MHz): δ = 2.03 (m_c, 1H), 2.24, 2.26 (m_c, s, 4H), 2.36, 2.39 (2s, 6H), 2.55 (m_c), 2.86, 2.92 (m_c, s, 4H), 3.03 (s, 3H), 5.39 (dd, 1H), 6.63 (s, 4H), 7.26 (m_c, 3H), 7.47 (m_c, 1H), 7.86 (s, 1H). The salt of the title compound with fumaric acid was added portionwise to a stirred mixture of sodium bicarbonate (10.5 g, 125 mmol), water (120 ml) and dichloromethane (200 ml). Stirring was continued until a clear biphasic mixture was obtained. The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 30 ml). The combined organic phases were washed with water (2 × 30 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue was dried in vacuo. A foamy solid (8.8 g) was obtained which was treated with diethyl ether (80 ml). The emulsion was warmed to 50 °C and, gradually, crystallization of the title compound occurred. The slurry was stirred for 1 h at room temperature. The crystals were isolated by filtration, washed with diethyl ether (15 ml) and dried in vacuo. The title compound was isolated in the form of a colourless solid (7.8 g, 48% yield, 56% corrected yield, 99.3% ee): mp 178–180 °C (diethyl ether); determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 3.7 min/0.3 area-%, RT [(9*S*)-enantiomer] = 4.4 min/98.1 area-%, 99.3% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.04 (m_c, 1H), 2.25, 2.30, 2.35, 2.39 (s, m_c, 2s, 10H) 2.56 (m_c), 2.85, 2.91, 3.02 (m_c, 2s, 7H), 5.37 (d, 1H), 7.28 (m_c, 3H), 7.47 (m_c, 1H), 7.79 (s, 1H); HRMS (ESI) *m*/*z* $C_{22}H_{26}N_3O_2$ $[M+H]^+$ calcd: 364.2020. Found: 364.2009. Anal. Calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.39; H, 7.16; N, 11.05.

4.26. (9*S*)-9-(4-Fluorophenyl)-2,3-dimethyl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 54

In a flame-dried flask filled with argon, diol **46** (1.20 g, 3.1 mmol, 98.6% ee) was suspended in dry THF (18 ml). After the addition of triphenylphosphine (1.22 g, 4.7 mmol) and the dropwise addition of DIAD (0.95 g, 4.7 mmol) a dark-green solution was obtained which was stirred for 30 min at room temperature. More triphenylphosphine (0.39 g, 1.5 mmol) and DIAD (0.30 g, 1.5 mmol) were added and stirring was continued for 15 min. The reaction solution was concentrated under reduced pressure and the crude product (5 g) was purified by column chromatography [70 g of silica gel, eluant: dichloromethane/methanol = 100:1 (v/v)]. Evaporation of the corresponding fractions furnished a green solid (1 g), which was suspended in acetone (1 ml) and diethyl ether (15 ml). The precipitate was removed by filtration, washed with diethyl ether and dried in vacuo. The title compound was isolated in 48% yield (0.55 g of a colourless solid). The mother liquor was concentrated and the obtained residue (400 mg) was purified by column chromatography [15 g of silica gel, eluant: ethyl acetate, then ethyl acetate/methanol = 10:1 (v/v)] and subsequent washing with diethyl ether (5 ml). This yielded another 130 mg of the title compound (60% overall yield, 98.2–98.4% ee). mp 258–260 °C; determination of the enantiomeric excess by HPLC (column: 250 × 4.6 mm CHIRALPAK® AD-H 5 μm; mobile phase: ethanol/methanol = 1:1 (v/v) with 0.1% of diethylamine; flow rate: 1 ml/min; 35 °C, detection at 243 nm): RT [(9*R*)-enantiomer] = 4.1 min/0.8 area-%, RT [(9*S*)-enantiomer] = 4.9 min/98.8 area-%, 98.4% ee; determination of the enantiomeric excess by CE (method A): MT [(9*S*)-enantiomer] = 17.6 min/99.1 area-%; MT [(9*R*)-enantiomer] = 18.0 min/0.9 area-%; 98.2% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.12 (m_c, 1H), 2.26 (m_c, s, 4H), 2.35 (s, 3H), 2.42 (m_c), 2.81, 2.88 (m_c, s, 4H), 3.01 (s, 3H), 5.27 (dd, 1H), 7.26 (t, 2H), 7.53 (dd, 2H), 7.79 (s, 1H); HRMS (ESI) *m*/*z* $C_{21}H_{23}FN_3O_2$ $[M+H]^+$ calcd: 368.1769. Found: 368.1758.

4.27. (9*S*)-2,3-Dimethyl-9-thiophen-2-yl-7*H*-8,9-dihydropyrano[2,3-*c*]-imidazo[1,2-*a*]pyridine-6-carboxylic acid dimethylamide 55

In a flame-dried flask filled with argon, diol **47** (1.80 g, 4.8 mmol, 99.2% ee) was suspended in dry dichloromethane (30 ml). After the addition of triphenylphosphine (1.90 g, 7.2 mmol) and the dropwise addition of DIAD (1.50 g, 7.4 mmol), a green solution was obtained which was stirred for 45 min at room temperature. More triphenylphosphine (0.60 g, 2.3 mmol) and DIAD (0.30 g, 2.5 mmol) were added and stirring was continued for 20 min. The reaction mixture was concentrated under reduced pressure to a volume of 15 ml and loaded on a column packed with silica gel (50 g). The by-products were eluted with dichloromethane/methanol = 100:1 (v/v) and the polarity of the eluant was increased to 20:1 (v/v). Evaporation of the corresponding fractions furnished a yellow-brown solid (0.62 g), which was suspended in acetone (2 ml). After a period of 1 h, the precipitate was isolated by filtration, washed with acetone (0.5 ml) and diethyl ether (8 ml) and dried in vacuo. The title compound was isolated in 22% yield (0.37 g of a colourless solid, 84.0% ee): mp 237–238 °C; determination of the enantiomeric excess by CE (method A): MT [(9*R*)-enantiomer] = 15.7 min/8.0 area-%; MT [(9*S*)-enantiomer] = 16.1 min/92.0 area-%; 84.0% ee; ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.25, 2.26, 2.34 (s, m_c, s, 8H), 2.53 (m_c), 2.73, 2.87 (m_c, s, 4H), 3.01 (s, 3H), 5.56 (dd, 1H), 7.08 (dd, 1H), 7.23 (br d, 1H), 7.57 (dd, 1H), 7.79 (s, 1H); HRMS (ESI) *m*/*z* $C_{19}H_{22}N_3O_2S$ $[M+H]^+$ calcd: 356.1427. Found: 356.1415. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 64.20; H, 5.95; N, 11.82; S, 9.02. Found: C, 64.04; H, 6.02; N, 11.70; S, 8.93.

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References

1. Modlin, I. M.; Sachs, G. *Acid Related Diseases: Biology and Treatment*; Schnetztor: Konstanz, 1998.
2. *Heartburn, hiatal hernia, and gastroesophageal reflux disease (GERD)*; NIH Publication No. 03-0882, June 2003; http://digestive.niddk.nih.gov/ddiseases/pubs/gerd/index.htm.
3. *H. pylori and peptic ulcer*; NIH Publication No. 05-4225, October 2004; http://digestive.niddk.nih.gov/ddiseases/pubs/hpylori/index.htm.
4. Parsons, M. E.; Keeling, D. J. *Exp. Opin. Invest. Drug* **2005**, *14*, 411–421.
5. Fass, R.; Shapiro, M.; Dekel, R.; Sewell, J. *Aliment. Pharmacol. Ther.* **2005**, *22*, 79–94.
6. Vakil, N. *Aliment. Pharmacol. Ther.* **2004**, *19*, 1041–1049.
7. Andersson, K.; Carlsson, E. *Pharmacol. Ther.* **2005**, *108*, 294–307.
8. Palmer, A. M.; Grobbel, B.; Jecke, C.; Brehm, C.; Zimmermann, P. J.; Buhr, W.; Feth, M. P.; Simon, W.-A.; Kromer, W. *J. Med. Chem.* **2007**, *50*, 6240–6264.
9. Buhr, W.; Chiesa, M. V.; Zimmermann, P. J.; Brehm, C.; Simon, W.-A.; Kromer, W.; Postius, S.; Palmer, A. Patent application WO 2005/058325.
10. Palmer, A. M.; Nettekoven, U. *Tetrahedron: Asymmetry* **2007**, *18*, 2381–2385.
11. Zimmermann, P. J.; Brehm, C.; Chiesa, M. V.; Buhr, W.; Palmer, A.; Nettekoven, U. Patent application WO 2005/058894.
12. Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681.
13. Lipshutz, B. H.; Lower, A.; Kucejko, R. J.; Noson, K. *Org. Lett.* **2006**, *8*, 2969–2972.
14. Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, *18*, 2943–2958.
15. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546.
16. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
17. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
18. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
19. Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061.
20. Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931–7944.

21. Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.
22. Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503.
23. BINAP: 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Xyl-BINAP: 2,2′-bis(di-3,5-xylylphosphanyl)-1,1′-binaphthyl, DPEN: 1,2-diphenylethylenediamine, DAIPEN: 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.
24. Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676.
25. Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417–10418.
26. Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086–1087.
27. Doucet, H.; Ohkuma, T.; Murata, K.; Yokazawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem.* **1998**, *110*, 1792–1796.
28. Strem—Chemicals for Research: Metals, Inorganics, and Organometallics, Catalog No. 20, 2004–2006, www.strem.com.
29. Palmer, A. M.; Zanotti-Gerosa, A. unpublished results.
30. Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151.
31. P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridinyl, Tol-P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis[di(*p*-tolyl)phosphino]-3,3′-bipyridinyl, Xyl-P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridinyl.
32. Wu, J.; Chen, H.; Kwok, W. H.; Lam, K. H.; Zhou, Z. Y.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539–1543.
33. Wu, J.; Chen, H.; Kwok, W.; Guo, R.; Zhou, Z.; Yeung, C.; Chan, A. S. C. *J. Org. Chem.* **2002**, *67*, 7908–7910.
34. Wu, J.; Ji, J.-X.; Guo, R.; Yeung, C.-H.; Chan, A. S. C. *Chem. Eur. J.* **2003**, *9*, 2963–2968.
35. Palmer, A.; Buhr, W.; Zimmermann, P. J.; Brehm, C.; Chiesa, M. V.; Zanotti-Gerosa, A. Patent application WO 2007/141253.
36. Set-up 1: The substrate and the catalyst were added into a glove liner, the vessel was sealed and purged with nitrogen. The solvent and a solution of the base were added and the reactor was pressurized with hydrogen. Set-up 2: The hydrogenation catalyst was added to a solution of the ketone and the base. In order to minimize the exposure of the catalyst to the base, it is recommendable that the solution of the catalyst is added last and hydrogen pressure is applied immediately afterwards.
37. Chaplin, D.; Harrison, P.; Henschke, J. P.; Lennon, I. C.; Meek, G.; Moran, P.; Pilkington, C. J.; Ramsden, J. A.; Wakins, S.; Zanotti-Gerosa, A. *Org. Process Res. Dev.* **2003**, *7*, 89–94.
38. European Medicines Agency Guidelines, www.emea.europe.eu.
39. Ekman, K.; Peltonen, R.; Sundell, M. Patent application WO 02/36648.
40. Buckley, S. *Speciality Chem. Mag.* **2002**, *22*, 12–13.
41. Danks, M. *Speciality Chem. Mag.* **2007**, *27*, 54–55.
42. *Be Selective—The Catalyst Technical Handbook*; Johnson Matthey Catalysts, 2005; http://www.jmcatalysts.com/pct.
43. However, complete transformation cannot always be accomplished by addition of fresh catalyst in the presence of spent catalyst.
44. In general, the hydrogen uptake curves are sigma-shaped. A slow induction period is followed by fast transformation of the substrate. Towards the end of the hydrogenation, the reaction rate slows down significantly.
45. Shi, Y.-J.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609–3611.
46. Dirlam, N. L.; Moore, B. S.; Urban, F. J. *J. Org. Chem.* **1987**, *52*, 3587–3591.