Highly enantioselective hydrogenation of quinolines under solvent-free or highly concentrated conditions†

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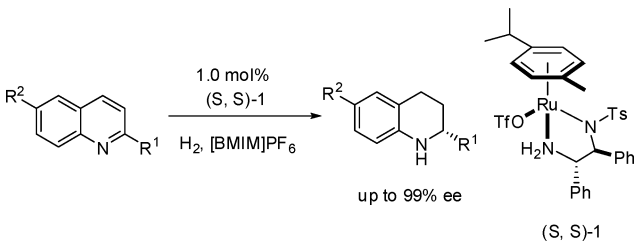
The phosphine-free chiral cationic Ru(OTf)(TsDPEN)(η⁶-cymene) complex was found to be an efficient catalyst for the enantioselective hydrogenation of quinolines under more environmentally friendly solvent-free or highly concentrated conditions. Excellent yields and enantioselectivities (up to 97% ee) were obtained at only 0.02–0.10 mol% catalyst loading.

The principles of green chemistry and green engineering dictate that avoiding the use of solvents is an important way to prevent the generation of waste.[1] For practical synthesis, reactions under solvent-free or highly concentrated conditions may have other advantages, including reduced energy consumption, decreased reaction times and considerable batch size reduction. Therefore, much research effort has been devoted to the development of solvent-free or highly concentrated reactions.[2] Among them, however, relatively few examples concerning solvent-free and concentrated catalytic asymmetric reactions have been reported so far.[2c,3,4] This is not surprising because asymmetric catalytic processes are usually highly sensitive to solvent and concentration of substrates. For solvent-free catalytic reactions, the reaction medium changes significantly as reagents and substrates are converted to products. Therefore, it is still a big challenge to develop highly enantioselective solvent-free and concentrated catalytic reactions. In particular, asymmetric hydrogenation of heteroaromatic compounds under solvent-free conditions is expected to be more difficult due to the potential poisoning of the catalysts by the substrates and/or the reduced products.

Transition metal-catalyzed asymmetric hydrogenations have been extensively studied, and are considered a versatile method for the preparation of optically active compounds.[5] Although a variety of chiral Rh, Ru, and Ir complexes have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines, most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[6] A few successful examples of the asymmetric hydrogenation of quinolines have recently been reported.[7] Iridium complexes containing chiral diphosphine[7a–c] or diphosphinite ligands,[7d] and P, N ligands[7e,f] have been found to be effective in the hydrogenation of 2-substituted quinolines. In most cases, however, good to excellent enantioselectivity and activity could only be obtained by using iodine as additive, and often at a low substrate-to-catalyst ratio (S/C) of 100. From a practical application viewpoint, it is highly desirable to develop air-stable phosphine-free catalysts for such reactions.

In comparison with chiral diphosphines, chiral diamine ligands are more readily available and air-stable.[8] Their Ru, Rh and Ir complexes have been widely used in the asymmetric transfer hydrogenation of ketones.[9] However, only a few of them were found to be capable of activating molecular hydrogen.[10,11] Recently, Noyori and Ohkuma reported that chiral Ru(OTf)(TsDPEN)(η⁶-cymene) and Cp*Ir(OTf)(MsDPEN) [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine; TfO^- = trifluoromethanesulfonate; Cp* = pentamethylcyclopentadienyl; MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine] complexes could be used for the asymmetric hydrogenation of prochiral ketones under slightly acidic conditions.[11] Later on, we found that ruthenium complex **1** is also an efficient catalyst for asymmetric hydrogenation of quinolines in pure ionic liquid with high enantioselectivity (Scheme 1).[12] Herein, we report our continuing effort on developing a more efficient process for this difficult transformation. Unlike the reported asymmetric hydrogenation of quinolines employing organic solvents, it was found that reactions under solvent-free or highly concentrated conditions provided the tetrahydroquinoline derivatives with much higher reactivity and excellent enantioselectivity at only 0.10–0.02 mol% catalyst loading.



Scheme 1 Asymmetric hydrogenation of quinolines catalyzed by Ru-catalyst (*S*,*S*)-**1** in $[BMIM]PF_6$ (BMIM=1-*n*-butyl-3-methylimidazolium).

We initially focused on the evaluation of the substrate concentration effects in the asymmetric hydrogenation by using 2-methylquinoline (**2a**) as a model substrate and methanol as the solvent.[8a] As shown in Table 1, when the reaction was run at 0.2 mol L^{-1} substrate concentration in methanol, decreasing the

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Table 1 Comparison of the asymmetric hydrogenation of 2-methylquinoline **2a** catalyzed by (*S*,*S*)-**1** in MeOH and under solvent-free conditions[a]

Entry	S/C	Solvent	Time/h	Conv. (%)[b]	ee (%)[c]
1	200	MeOH (0.2 M)	4	29	95
2	500	MeOH (0.2 M)	12	12	94
3	1000	MeOH (0.2 M)	24	<5	N. D.
4	1000	MeOH (2.0 M)	24	38	95
5	1000	MeOH (2.0 M)	48	76	95
6	200	Solvent free	4	>95	97
7	500	Solvent free	12	>95	96
8	1000	Solvent free	24	95	96
9[d]	5000	Solvent free	24	57	93
10[e]	100	Solvent free	20	50	77

[a] Reaction conditions: 0.2–2.0 mmol **2a** in 1 ml MeOH or under solvent-free conditions, 50 atm H_2, rt. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis with Chiralpak OJ-H Column, the product was in the *S*-configuration. [d] 0.1 mol% TfOH was used as an additive. [e] Ir-catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and P-Phos in combination with 5 mol% I_2 used as additive.

Table 2 Temperature and hydrogen pressure effect on the asymmetric hydrogenation of **2a** under solvent-free conditions[a]

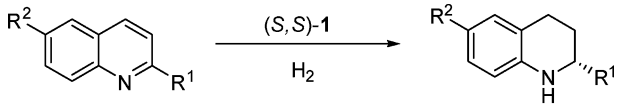
Entry	Temp./°C	H_2/atm	Time/h	Conv. (%)[b]	ee (%)[c]
1	0	50	24	23	97
2	25	50	24	>95	96
3	50	50	8	>95	94
4	80	50	4	60	90
5	25	80	12	100	96
6	25	50	12	86	96
7	25	20	12	46	96
8	25	1	24	6	96

[a] Reaction conditions: 2.0 mmol **2a**, 0.1 mol% (*S*,*S*)-**1**. [b] Determination by ^{1}H NMR. [c] Determined by chiral HPLC analysis.

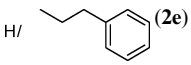
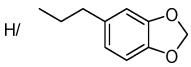
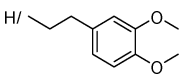
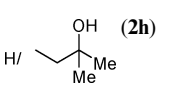
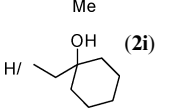
catalyst loading resulted in a significant decrease in reactivity (entries 1–3). It was noted that a higher conversion was obtained when increasing the substrate concentration from 0.2 to 2.0 mol L^{-1} at 0.1 mol% catalyst loading (entries 4 and 5). Thus, we speculated that the employment of solvent-free conditions would further increase the reactivity and allow a reduction in catalyst loading. To our delight, the reaction proceeded efficiently under solvent-free conditions in quantitative conversion with a slightly higher enantioselectivity as compared to those obtained in methanol under otherwise the same conditions (entries 6–8). *Remarkably, even when the catalyst loading was further reduced to 0.02 mol%, the reaction still gave the product in 57% conversion with 93% ee in the presence of 0.1 mol% TfOH.* To the best of our knowledge, this is the first example of highly enantioselective hydrogenation of heteroaromatic compounds under solvent-free conditions. In contrast, the same reaction catalyzed by the reported Ir(P-Phos)/I_2 catalytic system[7b] under solvent-free conditions at high catalyst loading (1.0 mol%) gave only 50% yield with 77% ee (entry 10).

We then examined the effects of the reaction temperature and hydrogen pressure on the solvent-free asymmetric hydrogenation of **2a**, and the results are listed in Table 2. It was found that increasing the temperature led to a high conversion rate but at a cost of slightly lower enantioselectivity (entries 1–4). Notably, a similar high enantioselectivity was achieved at various hydrogen pressures although a low conversion was observed by decreasing the hydrogen pressure (entries 5–8).

Table 3 Asymmetric hydrogenation of quinolines catalyzed by (*S*,*S*)-**1** under solvent-free or highly concentrated conditions[a]



2a~2k **3a~3k**

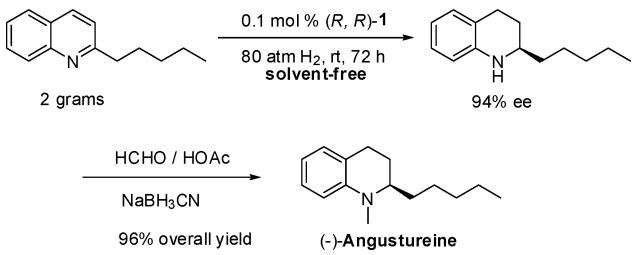
Entry	R^1/R^2	H_2/atm; Temp./°C	Yield (%)[b]	ee (%)[c]
1	H/Me (**2a**)	50; 25	99	97
2	H/Et (**2b**)	50; 25	98	95
3	H/n-Pr (**2c**)	50; 25	97	94
4	H/n-Pentyl (**2d**)	80; 25	99	94
5[d]	 (**2e**)	50; 50	95	92
6[d]	 (**2f**)	80; 80	99	87
7[d]	 (**2g**)	80; 80	98	85
8[d]	 (**2h**)	80; 50	92	97
9[d]	 (**2i**)	80; 80	98	97
10[d]	MeO/Me (**2j**)	80; 80	99	93
11[d]	F/Me (**2k**)	80; 80	96	90

[a] Reaction conditions: 1.0–2.0 mmol substrate, 0.1 mol% (*S*,*S*)-**1**, 24–60 h. [b] Isolated yield. [c] Determined by HPLC analysis with Chiralpak OJ-H (or OD-H and AS-H) Column. [d] 0.1 mL 2-propanol and 0.1 mol% TfOH were added.

Next, a variety of 2-substituted quinoline derivatives (**2a–2k**) were hydrogenated in the presence of 0.1 mol% of catalyst (*S*,*S*)-**1** under solvent-free or highly concentrated conditions. Nearly quantitative yields and high enantioselectivities (up to 97% ee) were obtained in all cases (Table 3). In the case of liquid substrates, 2-alkyl substituted quinolines, the reactions proceeded smoothly under solvent-free conditions. It was found that the length of side chain slightly influenced the enantioselectivity and reactivity (entries 1–4). For the solid substrates, hydrogenation was carried out under highly concentrated conditions (10 mol L^{-1}) in the presence of 0.1 mol% of TfOH. As compared with 2-alkyl substituted quinolines, 2-phenethyl substituted quinolines also gave high yield, albeit with slightly lower enantioselectivities (entries 5–7). It was noted that quinolines with a free hydroxyl group on the side chain could be hydrogenated smoothly in high yield with excellent enantioselectivities (entries 8–9). However, the presence of substituted groups at C-6 led to slightly lower enantioselectivities (entries 10 and 11).

Finally, we applied this attractive new protocol to the synthesis of a biologically active tetrahydroquinoline alkaloid, angustureine.[13] Asymmetric hydrogenation of 2-pentyl

substituted quinoline was carried out on a gram scale at a catalyst loading of 0.1 mol%, giving the tetrahydroquinoline derivative in quantitative conversion with 94% ee. Subsequent *N*-methylation of the hydrogenated product afforded the desired natural product in 96% overall yield (Scheme 2).



Scheme 2 Synthesis of naturally occurring tetrahydroquinoline alkaloid, (−)-angustureine.

In conclusion, the first highly enantioselective hydrogenation of quinolines catalyzed by phosphine-free chiral cationic Ru-TsDPEN catalyst has been achieved under more environmentally friendly solvent-free or highly concentrated conditions at low catalyst loading (low to 0.02 mol%). This new method provides a practical synthetic approach to optically active tetrahydroquinoline derivatives.

Acknowledgements

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