Asymmetric Catalysis

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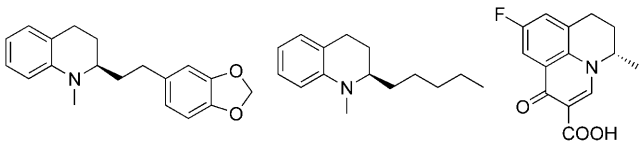
pH-Regulated Asymmetric Transfer Hydrogenation of Quinolines in Water**

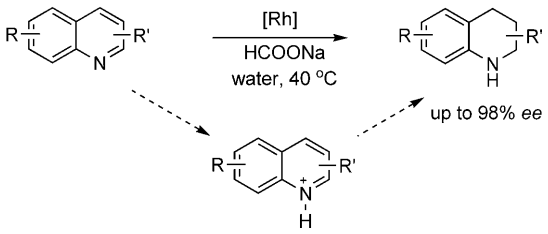
*Chao Wang, Chaoqun Li, Xiaofeng Wu, Alan Pettman, and Jianliang Xiao**

1,2,3,4-Tetrahydroquinolines exist as key structural elements in many natural products and have found broad commercial application.[1] In particular, optically pure tetrahydroquinolines are commonly present in alkaloids and are required in pharmaceutical and agrochemical synthesis. Representative examples include the bioactive alkaloids (+)-galipinine[2] and (−)-augustureine,[2b,3] and the antibacterial drug (*S*)-flumequine.[2b]



The most convenient route to chiral tetrahydroquinolines is the asymmetric reduction of quinolines. Successful examples of their hydrogenation by H_2 with organometallic catalysts have been reported.[4] However, although enantioselectivities of up to 99% *ee* have been demonstrated, these catalysts usually require a high hydrogen pressure. In recently reported organocatalytic asymmetric reduction reactions of quinolines with the Hantzsch ester as the hydrogen source, excellent enantioselectivities were observed for 2-aryl substituted quinolines.[5] Surprisingly, there have been no reports of the asymmetric transfer hydrogenation (ATH) of quinolines with metal catalysts, although economical and environmentally benign hydrogen sources, such as isopropanol or formate, are generally used for ATH reactions, and ATH is operationally simpler than hydrogenation.[6,7] Herein we describe the ATH of quinolines[8] in water. The reactions were carried out in air, and excellent enantioselectivities were observed for a wide range of substrates (Scheme 1).

The use of water as a reaction medium has been under intense investigation.[9] Apart from potential economic and ecological gains, water can offer new reactivity and selectivity patterns.[9,10] In this context, we and other research groups have reported successful ATH reactions of ketones and imines in neat water.[6g,11–13] In particular, a combination of the unmodified Noyori ligand Ts-dpen (Ts-dpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)[14] and [{$RuCl_2$(*p*-cymene)}$_2$] or [(Cp*MCl_2)$_2$] (M = Rh, Ir) led to the efficient reduction of aryl ketones with HCOONa in water. Among these catalysts, the Rh–Ts-dpen catalyst showed the highest activity and selectivity.[11c]



Scheme 1. ATH of quinolines in water and a possible intermediate.

We chose to use presynthesized Rh–Ts-dpen as the catalyst[15] and began our study of quinoline reduction by examining the ATH of a model substrate, 2-methylquinoline (**1a**: R = H, R′ = 2-CH_3), with HCOONa in water (Scheme 1). Disappointingly, only 17% conversion was observed at 40 °C in 12 h with a substrate/catalyst (S/C) ratio of 100:1 (**1a**: 0.5 mmol, HCOONa: 10 equiv, water: 5 mL). However, the enantioselectivity was excellent: the product was obtained with 96% *ee*.

In our previous study on the ATH of ketones in water, the pH value of the solution was found to have a critical effect on the reaction rate.[11b,c] In the present quinoline reduction, the initial pH value of the solution was approximately 8. However, recent studies on asymmetric hydrogenation suggest that quinoline is hydrogenated through an ionic mechanism in its protonated form (Scheme 1).[4g,5a,16] Support for an ionic hydrogenation[17] mechanism of this type was also found in our recent studies on asymmetric imine hydrogenation.[18] Assuming that quinoline is reduced by a Rh^{III}–H hydride in this way, while bearing in mind that the pK_a value of protonated **1a** is 5.4, one would not expect the present ATH to take place under basic conditions. We therefore examined the effect of the pH value of the solution on the

[*] C. Wang, C. Q. Li, Dr. X. F. Wu, Prof. J. L. Xiao
Liverpool Centre for Materials and Catalysis
Department of Chemistry
University of Liverpool, Liverpool L69 7ZD (UK)
Fax: (+44) 151-794-3589
E-mail: j.xiao@liv.ac.uk
Homepage: http://pcwww.liv.ac.uk/~jxiao
Dr. A. Pettman
Chemical R & D, Global Research & Development, Pfizer
Sandwich, Kent CT13 9NJ (UK)

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ATH rate. We adjusted the pH value by altering the HCOOH/HCOONa ratio and found that the ATH of **1a** was indeed strongly affected by the pH value of the solution, with the maximum conversion in 0.5 h observed at pH 5 (Figure 1). However, the enantioselectivity did not vary; the product was obtained consistently with 96% *ee*.

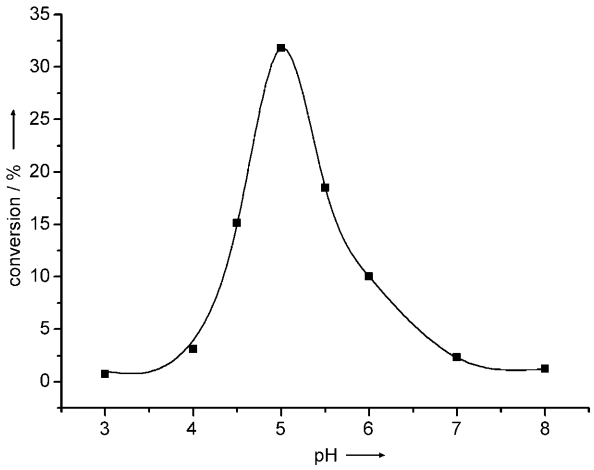
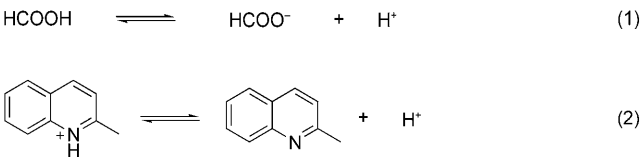


Figure 1. Effect of the initial pH value of the solution on the ATH of **1a** catalyzed by Rh–Ts-dpen. Reactions were carried out on a 0.5 mmol scale in a 2 M HCOOH/HCOONa buffer solution (5 mL) at 40 °C.

A plausible explanation for this volcano curve may be found in the two conflicting equilibria shown in Equations (1) and (2) that provide the reductant and substrate, respectively.



At high pH values (pH > 5.4), the concentration of protonated **1a** becomes low, whereas at low pH values (pH < 3.6), the concentration of formate decreases. Thus, a pH value between 3.6 and 5.4 would be expected to provide high concentrations of *both* reactants and could therefore lead to high reaction rates. However, other factors, such as the solution phase, might also play a role, as the ATH reaction mixture was homogeneous at pH 4 and became heterogeneous at higher pH values.

Having identified the best pH value, we then repeated the ATH of **1a** with the initial pH value of the solution set to 5. Somewhat surprisingly, the reduction did not reach completion even after a prolonged reaction time. We speculated that the pH value might vary significantly during the reaction and monitored the ATH by GC. The initial ATH rate was very fast when the reaction was started at pH 5 (Figure 2). However, the reaction stopped completely after approximately 60 min at less than 50% conversion. A change in the solution pH value, which quickly rose to 8 and hardly changed thereafter, accompanied this change in reaction rate. The enantioselectivity was constant throughout the reaction. Together with the results in Figure 1, these findings point to the rise in the solution pH value as the factor responsible for the decrease in the ATH rate with time, and so the necessity to control the pH value.

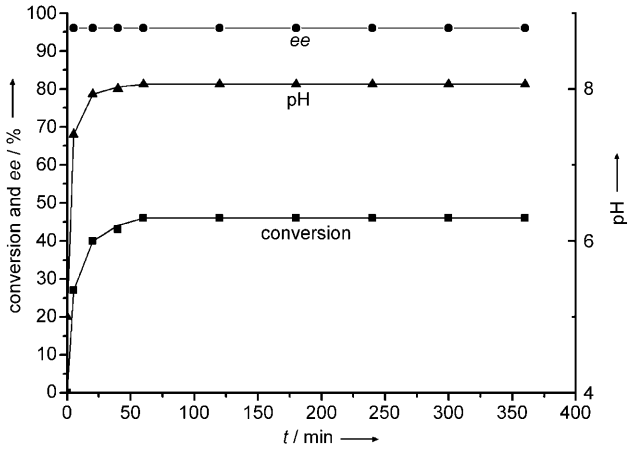
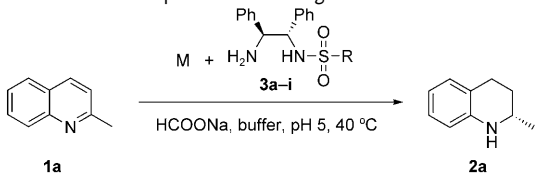


Figure 2. Conversion (■), pH value (▲), and enantioselectivity (●) with respect to time in the ATH of **1a** catalyzed by Rh–Ts-dpen. The ATH of **1a** (1 mmol) was carried out in a 2 M HCOOH/HCOONa buffer solution (10 mL) with an initial pH value of 5.

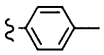
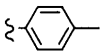
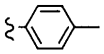
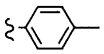
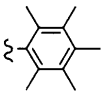
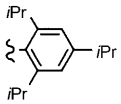
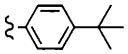
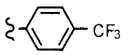
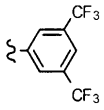
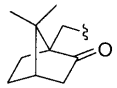
Buffered solutions provide a means to curb pH fluctuation. With a pK_a value of 3.6, however, the buffer capacity of the HCOOH/HCOONa pair used in this ATH is insufficient.[19] A better choice would be the HOAc/NaOAc system, which has its maximum buffer capacity at approximately pH 5 (the pK_a value of HOAc is 4.8).[19] When a 2 M HOAc/NaOAc buffer solution was used instead of neat water, the ATH of **1a** proceeded to 95% conversion in 3 h, with identical enantioselectivity to that observed in aqueous formate.

In the hope to further improve the ATH efficiency, we then examined different metal precursors and ligands for the ATH of **1a** at pH 5 with the HOAc/NaOAc buffer system by simply stirring a metal precursor, ligand, substrate, and HCOONa in the buffer solution. With Ts-dpen (**3a**) as the ligand, $[(Cp^*RhCl_2)_2]$ afforded the best results when compared with isoelectronic $[\{RuCl_2(p\text{-cymene})\}_2]$ and $[\{Cp^*IrCl_2\}_2]$ (Table 1, entries 1–3). The R group of the sulphonamide affects both the catalytic activity and the selectivity. Thus, increased steric hindrance led to diminished conversion and enantioselectivity (Table 1, entries 4–7). However, no improvement was observed when R was a small methyl group (Table 1, entry 12), and the electronic properties of the substituent had little effect (compare entries 4 and 9, Table 1). The best reactivity and enantioselectivity were observed with the 4-*tert*-butylphenyl-substituted ligand **3e** (Table 1, entry 8). On this basis, complex **4**, prepared from **3e** and $[(Cp^*RhCl_2)_2]$,[15] was chosen as the catalyst for the ATH of quinolines in an aqueous formate solution buffered to pH 5 with HOAc/NaOAc.

Table 1: Effect of metal precursors and ligands on the ATH of **1a**.[a]



1a **2a**

Entry	M	3	R	Conv.[b] [%]	*ee*[b] [%]
1	$[\{RuCl_2(p\text{-cymene})\}_2]$	**3a**		32	90
2	$[(Cp^*IrCl_2)_2]$	**3a**		88	11
3	$[(Cp^*RhCl_2)_2]$	**3a**		95	96
4	$[(Cp^*RhCl_2)_2]$	**3a**		49	96
5	$[(Cp^*RhCl_2)_2]$	**3b**		13	83
6	$[(Cp^*RhCl_2)_2]$	**3c**		12	74
7	$[(Cp^*RhCl_2)_2]$	**3d**		34	94
8	$[(Cp^*RhCl_2)_2]$	**3e**		55	97
9	$[(Cp^*RhCl_2)_2]$	**3f**		48	96
10	$[(Cp^*RhCl_2)_2]$	**3g**		31	94
11	$[(Cp^*RhCl_2)_2]$	**3h**		39	90
12	$[(Cp^*RhCl_2)_2]$	**3i**	CH_3	27	94

[a] Reaction conditions: **1a** (0.5 mmol), metal precursor (2.5 μmol), ligand (6 μmol), HCOONa (5 mmol), 2 M HOAc/NaOAc buffer solution (5 mL), 40 °C. The reaction time was 12 h for entries 1–3 and 0.5 h for entries 4–12. [b] The conversion and *ee* value of the product were determined by GC.

Various quinoline derivatives were subjected to ATH catalyzed by **4**. Excellent enantioselectivities and yields were observed for a range of substrates (Table 2). Thus, the ATH of **1a** afforded **2a** in 96% yield and with 97% *ee* in 6 h (Table 2, entry 1). Notably, the ATH was carried out in air, without degassing. When the reaction was performed under nitrogen, no significant difference in either the reduction rate or the enantioselectivity was observed. The chain length of the alkyl substituent at the 2-position had little effect on the enantioselectivity (Table 2, entries 1–6); the same was true for various substituents at 6- or 7-position (Table 2, entries 7–12). However, slightly lower yields resulted from the use of substrates with electron-rich substituents at the 6-position (Table 2, entries 11 and 12). Of particular note are the excellent *ee* values observed with this catalyst for quinolines with sterically more demanding substituents at the 2-position (Table 2, entries 13–19), although lower yields were encountered in some cases (Table 2, entry 15). The hydrogenation of some of these substrates, for example, 2-(4-methoxybenzyl)-quinoline (Table 2, entry 19), with H_2 was challenging.[4e,h] Furthermore, isolated C=C bonds were tolerated under these conditions (Table 2, entry 20); overreduction only happened after a prolonged reaction time of about 9 h.

A problem arose with the less basic, 2-phenyl-substituted substrate **1u**. When the precatalyst **4** was used at pH 5, only 30% conversion was observed in 24 h. However, when the buffered solution was adjusted to the lower pH value of 4, and the ligand **3g** was combined with $[(Cp^*RhCl_2)_2]$ to form the catalyst, **1u** was reduced to **2u** in 96% yield with 90% *ee*. Similar results were obtained with **1v** and **1w** (Table 2, entries 22 and 23). Asymmetric hydrogenation reactions of substrates of this type with H_2 and organometallic catalysts tend to proceed with lower enantioselectivities.[4] Also interesting is that 2,3-di-substituted quinolines were reduced with high enantioselectivity (Table 2, entries 24 and 25). The results suggest that if the ATH follows a 1,4-addition pathway,[4g,5a] the subsequent reduction of the iminium C=N double bond, which results from protonation of the enamine 1,4-addition product, is likely to occur by dynamic kinetic resolution.

In conclusion, we have developed the first organometallic ATH protocol for the asymmetric reduction of quinoline derivatives in water. Excellent enantioselectivities and good yields were observed under buffered conditions for a broad range of substrates, including those that were problematic for hydrogenation catalysts. This mild and operationally simple method provides a valuable alternative route to chiral tetrahydroquinolines and could be applicable to other heteroaromatic compounds as well.

Experimental Section

Typical procedure: A carousel reaction tube containing a magnetic stirring bar and the catalyst **4** (3 mg, 5 μmol), **1a** (72 mg, 0.5 mmol), and HCOONa (0.34 g, 5 mmol) in an aqueous solution of HOAc/NaOAc (2 M, 5 mL, pH 5) was sealed without degassing and placed in a carousel reactor. The reaction mixture was stirred at 40 °C for the time indicated, then cooled to room temperature and basified with an aqueous solution of KOH. The resulting mixture was extracted with diethyl ether (3 × 5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography. The enantioselectivity was determined by HPLC.

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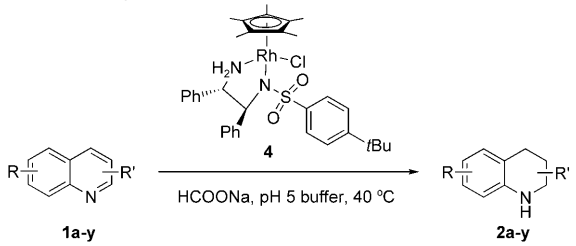
Table 2: ATH of quinolines with formate and **4** in buffered water.[a]



1a-y **2a-y**

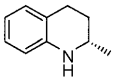
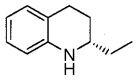
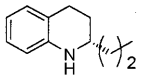
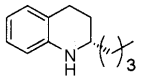
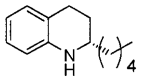
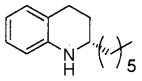
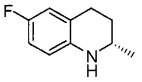
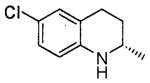
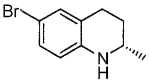
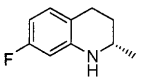
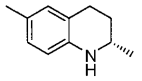
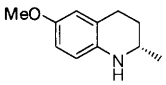
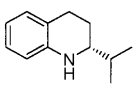
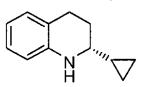
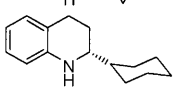
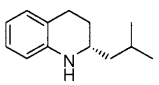
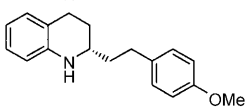
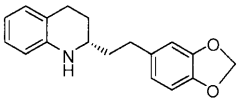
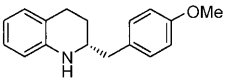
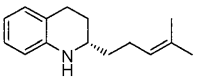
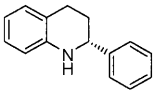
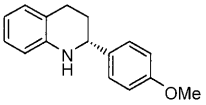
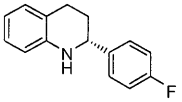
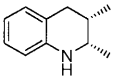
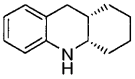
Entry		Product	Yield [%][b]	*ee* [%][c]
1	**2a**		96	97
2	**2b**		95	96
3	**2c**		93	97
4	**2d**		94	97
5	**2e**		95	97
6	**2f**		92	97
7	**2g**		96	96
8	**2h**		95	96
9	**2i**		96	95
10	**2j**		97	96
11	**2k**		91	96
12	**2l**		90	98
13	**2m**		86	91
14	**2n**		88	98
15[d]	**2o**		87	96
16	**2p**		97	97
17	**2q**		84	97

Table 2: (Continued)

Entry		Product	Yield [%][b]	*ee* [%][c]
18	**2r**		85	97
19	**2s**		80	96
20	**2t**		90	97
21[e]	**2u**		96	90
22[e]	**2v**		95	90
23[e]	**2w**		93	89
24[d]	**2x**		89	92 (4:1)[f]
25	**2y**		95	86 (99:1)[f]

[a] Reaction conditions: **1** (0.5 mmol), **4** (5 μmol), HCOONa (5 mmol), buffer solution (5 mL), 40 °C, 6–24 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis; the absolute configuration was assigned by comparison with literature data. [d] The reaction was carried out with 2 mol % of **4**. [e] Compound **3g** was used as the ligand at pH 4 in 2 M HOAc/NaOAc buffer solution (5 mL) with EtOAc (0.3 mL). [f] The diastereoselectivity is given in brackets.

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