Asymmetric Tandem Reduction of 2-(Aroylmethyl)quinolines with Phosphine-Free Ru-TsDPEN Catalyst

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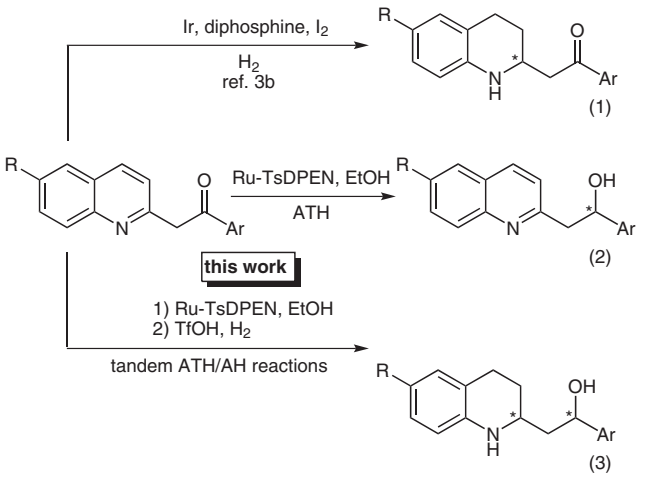
Abstract: The phosphine-free ruthenium complex containing chiral *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) showed excellent stereoselectivity in the tandem asymmetric reduction of 2-(aroylmethyl)quinolines. The reaction involves transfer hydrogenation of aromatic ketones and hydrogenation of quinolines, giving 1,2,3,4-tetrahydroquinoline derivatives with up to 99% ee and 95:5 dr.

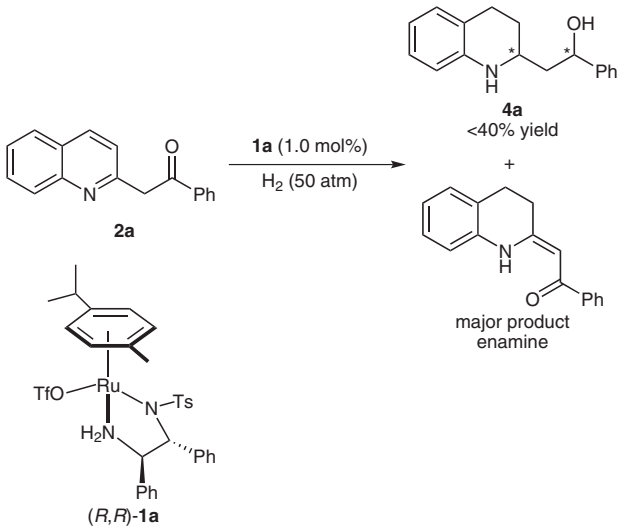
Key words: asymmetric catalysis, tandem reaction, quinolines, ruthenium, hydrogenation

Asymmetric hydrogenation of heteroaromatic compounds to give chiral heterocycles using inexpensive molecular hydrogen and a small amount of chiral transition-metal catalyst represents one of the most straightforward, efficient, and atom-economic methods available.[1] Representative examples including hydrogenation of quinolines,[2–4] indoles,[5a,b] pyrroles,[5c] furans,[5d] pyridines,[5e] isoquinolines,[5f] and quinoxalines[5g,h] have been reported. Among them, the Ir-catalyzed asymmetric hydrogenation of quinoline derivatives has attracted attention since the pioneering work reported by Zhou and co-workers.[1b,2] To date, a number of iridium complexes containing chiral diphosphine, diphosphinite or monophosphine ligands, or P,N ligands have been found to be effective in the hydrogenation of 2-substituted quinoline derivatives.[1b,2,3] Most recently, we demonstrated that the phosphine-free, chiral cationic Ru(OTf)(TsDPEN)(η^6-cymene) complex was an effective catalyst for the asymmetric hydrogenation of quinolines in ionic liquid or under solvent-free conditions, providing both excellent enantioselectivity and reactivity.[4]

2-(Aroylmethyl)quinolines contain both C=N and C=O functional groups and present ketoimine and enaminone tautomers in solution.[6] The selective and/or full asymmetric hydrogenation of both functional groups can provide new kinds of enantiomerically pure quinoline and 1,2,3,4-tetrahydroquinoline derivatives. Most recently, Zhou and co-workers first reported the selective asymmetric hydrogenation of the C=N bond in a range of 2-(aroylmethyl)quinolines using $[Ir(cod)Cl]_2$/MeO-BIPHEP/I_2 as catalyst with high enantioselectivity (Scheme 1, equation 1).[3b] Herein, we wish to report our preliminary results for the selective asymmetric transfer hydrogenation of the C=O bond (Scheme 1, equation 2), tandem reductions including asymmetric transfer hydrogenation (ATH) of the C=O bond, and asymmetric hydrogenation (AH) of the C=N bond (Scheme 1, equation 3) of a range of 2-(aroylmethyl)quinolines by using phosphine-free Ru-TsDPEN catalyst.[7]



Scheme 1 Asymmetric reduction of 2-(aroylmethyl)quinolines



Scheme 2 Asymmetric hydrogenation of 2-(benzoylmethyl)quinoline catalyzed by (*R*,*R*)-**1a**

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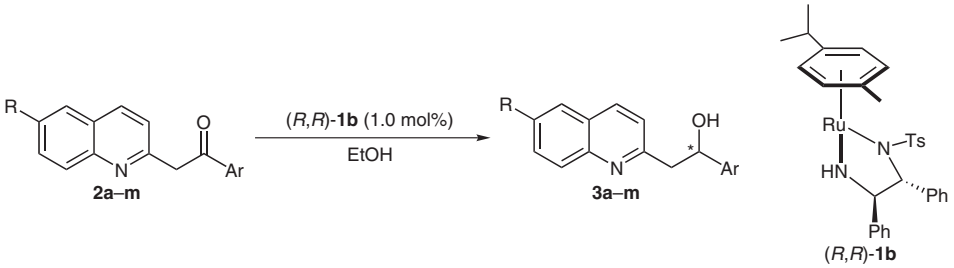
In our initial exploratory studies, Ru-TsDPEN (*R*,*R*)-**1a** was used as catalyst in the asymmetric hydrogenation of 2-(benzoylmethyl)quinolines (**2a**), because this catalyst has proven to be effective in the hydrogenation of both aromatic ketones[7b,c] and quinolines.[4] Although the expected chiral product, 2-(1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanol, was observed in high stereoselectivity (99% ee and 76:24 dr), the major product was found to be the enamine (*Z*)-2-(3,4-dihydroquinolin-2(1*H*)-ylidene)-1-phenylethanone (Scheme 2). In contrast to the Ir catalyst,[8] the Ru catalyst was found to be inactive in the hydrogenation of this enamine. After testing different reaction conditions, the yield of the chiral product was less than 40%, which was probably due to the existence of ketoimine and enaminone tautomers.

Considering the Ru-TsDPEN complexes to be powerful catalysts for ATH of aromatic ketones,[9] we then investigated the selective ATH of the C=O bond of 2-(aroylmethyl)quinolines. Chiral alcohols containing the quinoline unit are important chiral building blocks in organic synthesis and chiral drug production, for example, synthesis of the LTD_4 antagonist L-708,738 at Merck.[10] Firstly, ATH of **2a** was performed in the presence of 1.0 mol% (*R*,*R*)-**1b** by using methanol as both hydrogen source and solvent at room temperature for four hours. To our delight, the chiral alcohol **3a** was obtained as the sole product with 94% ee (Table 1, entry 1), suggesting that ATH of quinoline could not occur.[11] After screening a range of alcoholic solvents, ethanol was found to be the best choice for this reaction in terms of both enantioselectivity and reactivity (entries 1–4). Notably, complete conversion and

Table 1 Asymmetric Transfer Hydrogenation (ATH) of 2-(Aroylmethyl)quinolines[a]



Entry	R, Ar (Substrate)	Solvent	Yield (%)[b]	ee (%) (Config.)[c]
1	H, Ph (**2a**)	MeOH	35	94 (+)
2	H, Ph (**2a**)	EtOH	38	97 (+)
3	H, Ph (**2a**)	*i*-PrOH	35	87 (+)
4	H, Ph (**2a**)	*n*-BuOH	17	91 (+)
5	H, Ph (**2a**)	EtOH	96	97 (+)
6	H, *o*-$MeOC_6H_4$ (**2b**)	EtOH	91	67 (+)
7[d]	H, *o*-MeC_6H_4 (**2c**)	EtOH	90	84 (+)
8	H, *o*-FC_6H_4 (**2d**)	EtOH	87	73 (+)
9	H, *m*-$MeOC_6H_4$ (**2e**)	EtOH	94	99 (+)
10	H, *m*-MeC_6H_4 (**2f**)	EtOH	95	90 (+)
11	H, *m*-FC_6H_4 (**2g**)	EtOH	90	89 (+)
12	H, *p*-$MeOC_6H_4$ (**2h**)	EtOH	96	90 (+)
13	H, *p*-MeC_6H_4 (**2i**)	EtOH	97	91 (+)
14	H, *p*-FC_6H_4 (**2j**)	EtOH	84	89 (+)
15	MeO, Ph (**2k**)	EtOH	97	87 (+)
16	Me, Ph (**2l**)	EtOH	95	93 (+)
17	F, Ph (**2m**)	EtOH	89	85 (+)

[a] Reaction conditions: substrate (0.1 mmol), EtOH (1 mL), (*R*,*R*)-**1b** (1 mol%), 25 °C, 24 h, except for entries 1–4 (4 h).
[b] Isolated yields, except for entries 1–4 (conversion of **2a**).
[c] The ee values of the major isomer were determined by HPLC analysis with a chiral column (see the Supporting Information).
[d] With 2 mol% (*R*,*R*)-**1b**.

similar enantioselectivity was observed upon prolonged reaction time (entry 5).

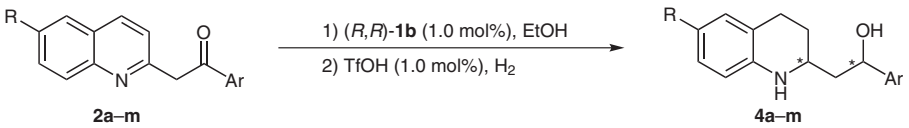
Under the optimal reaction conditions, ATH of a range of 2-(aroylmethyl)quinolines **2a**–**m** were then examined, and good to excellent enantioselectivities (67–99% ee) were obtained. It was found that both steric and electronic properties of the substituents on the phenyl ring of the substrates have a clear impact on enantioselectivity and reactivity (Table 1, entries 5–17). Introduction of a substituent into the *ortho* position of the phenyl ring of the aryl ketones led to a lower enantioselectivity (entries 6–8). ATH of **2c**, bearing an *o*-methyl group on the phenyl ring, required 2.0 mol% catalyst to achieve complete conversion (entry 7). Substrates bearing a fluorine substituent also exhibited low reactivity and/or enantioselectivity (entries 8, 11, 14 and 17). The highest enantioselectivity was observed in the ATH of **2e** bearing an *m*-methoxy group on the phenyl ring (entry 9).

Having achieved efficient ATH of 2-(aroylmethyl)quinolines, we further investigated AH of the reduced chiral quinoline by using **3a** as a standard substrate. Hydrogenation was carried out in ethanol with 1.0 mol% (*R*,*R*)-**1a**. The reaction occurred smoothly at room temperature under 50 atm H_2 in 8 h, providing 1,2,3,4-tetrahydroquinoline derivative **4a** with excellent enantioselectivity (>99% ee). On the basis of this exciting result, and on the fact that (*R*,*R*)-**1a** can be generated in situ from the reaction of (*R*,*R*)-**1b** with one equivalent TfOH,[7b] we reasoned that sequential ATH of a ketone and AH of quinoline could be carried out in a one-pot manner. We then conducted the tandem reductions using **2a** as a standard substrate. After the reaction was carried out in ethanol with 1.0 mol% (*R*,*R*)-**1b** in 24 h, 1.0 mol% TfOH was added into the reaction mixture under nitrogen atmosphere. The autoclave was then pressurized to 50 atm with hydrogen and stirred at room temperature in 12 h. Gratifyingly, complete conversion was observed, and **4a** was obtained as the sole product with excellent stereoselectivity (>99% ee, >95:5 dr; Table 2, entry 1).

Finally, the scope of the reaction with 2-(aroylmethyl)quinolines was briefly investigated (Table 2). In all cases, the tandem reactions proceeded smoothly in high yields and with excellent enantioselectivity (>99%) and diastereoselectivity (88:12 to >95:5). Introducing a substituent into the *ortho* position of the phenyl ring of aryl ketones led to relatively low yields and diastereoselectivities (entries 2–4). Substrates bearing fluorine substituents also showed low reactivity.

In conclusion, we have successfully developed a selective asymmetric transfer hydrogenation of the C=O bond of

Table 2 Asymmetric Tandem Reduction (ATH/AH) of 2-(Arocylmethyl)quinolines[a]



2a–m **4a–m**

Entry	R, Ar (Substrate)	Yield (%)[b]	dr[c]	ee (%) (config.)[d]
1	H, Ph (**2a**)	94	>95:5	>99 (+)
2	H, *o*-$MeOC_6H_4$ (**2b**)	89	88:12	99 (+)
3[e]	H, *o*-MeC_6H_4 (**2c**)	89	90:10	>99 (+)
4	H, *o*-FC_6H_4 (**2d**)	85	88:12	>99 (+)
5	H, *m*-$MeOC_6H_4$ (**2e**)	94	93:7	99 (+)
6	H, *m*-MeC_6H_4 (**2f**)	92	93:7	99 (+)
7	H, *m*-FC_6H_4 (**2g**)	88	91:9	>99 (+)
8	H, *p*-$MeOC_6H_4$ (**2h**)	93	93:7	99 (+)
9	H, *p*-MeC_6H_4 (**2i**)	95	94:6	>99 (+)
10	H, *p*-FC_6H_4 (**2j**)	80	91:9	99 (+)
11	MeO, Ph (**2k**)	94	95:5	>99 (+)
12	Me, Ph (**2l**)	91	95:5	>99 (+)
13	F, Ph (**2m**)	84	95:5	>99 (+)

[a] Reaction conditions: substrate (0.1 mmol) in EtOH (1 mL), (*R*,*R*)-**1b** (1 mol%), 25 °C, 24 h; then, TfOH (1 mol%), H_2 (50 atm), 12 h.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] The ee value of the major diastereomer was determined by HPLC analysis with a chiral column (see the Supporting Information).
[e] With 2 mol% (*R*,*R*)-**1b** and 2 mol% TfOH.

2-(aroylmethyl)quinolines, and the tandem ATH/AH reductions of 2-(aroylmethyl)quinolines with excellent stereoselectivity by using phosphine-free Ru-TsDPEN complex as the catalyst.[12] Further application of this catalytic system in the asymmetric reduction of other heteroaromatics and prochiral imines is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(12) **Typical procedure for the Ru-catalyzed asymmetric ATH/AH reactions**: Into a 50 mL glass-lined stainless steel reactor with a magnetic stirring bar was charged (*R*,*R*)-**1b** (0.6 mg, 0.001 mmol), substrate **2a** (24.7 mg, 0.1 mmol) and degassed EtOH (1 mL) under a nitrogen atmosphere, and the mixture was stirred at r.t. for 24 h. Then, to the reaction mixture was added a solution of 1.0 M TfOH in EtOH (100 μL, 0.001 mmol, 1 mol% *cf* substrate) under a nitrogen atmosphere. The autoclave was closed, and H_2 was initially introduced into the autoclave at a pressure of 50 atm, before being reduced to 1 atm. After this procedure was repeated three times, the autoclave was pressurized with H_2 to 50 atm. Subsequently, the mixture was stirred under this H_2 pressure at r.t. for another 12 h. After carefully releasing the hydrogen, the mixture was concentrated to afford the crude product. The conversion and diastereoselectivity were determined by ^{1}H NMR analysis of the crude product. Further purification was performed with a silica gel column (PE–CH_2Cl_2, 1:1) to give the pure product, (+)-1-phenyl-2-(1,2,3,4-tetrahydroquinolin-2-yl)ethanol (**4a**). Isolated yield: 94%; >95:5 dr; >99% ee; $[\alpha]_D^{20}$ +67.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 7.00–6.95 (m, 2 H), 6.67–6.62 (m, 1 H), 6.49 (d, *J* = 7.8 Hz, 1 H), 5.02 (t, *J* = 6.6 Hz, 1 H), 3.55–3.47 (m, 1 H), 2.88–2.69 (m, 2 H), 1.97–1.90 (m, 3 H), 1.88–1.81 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.34, 143.14, 128.30, 127.56, 126.61, 125.70, 124.69, 120.69, 116.73, 113.99, 71.07, 47.79, 43.67, 26.95, 25.15; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}NO$: 254.15394; found: 254.15385.