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Efficient asymmetric transfer hydrogenation of *N*-sulfonylimines on water

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ABSTRACT

An efficient and green approach for synthesis of optically active amines was developed via asymmetric transfer hydrogenation of *N*-sulfonyl ketimines catalyzed by the chiral and lipophilic rhodium-amido complex on water. Higher reactivity and enantioselectivity were observed on the hydrogenation of the solid substrate in an aqueous suspension compared to organic homogeneous phases. In the heterogeneous aqueous reaction, the reactivity depends on stirring speed and the recrystallized conditions of the solid substrate.

1. Introduction

Presently, there is an intense interest in developing greener chemistry for both laboratory and industrial applications. Replacement of organic solvents and especially chlorinated ones, with greener ones is an important question for green chemistry.[1] Water is an attractive solvent for organic reactions because it is low cost, safer to operate (non-flammable, non-toxic), and negligible impact for the environment, and often shows interesting features like enhanced reaction rate and selectivity (chemo-, regio-, stereo-, even enantio-) if compared to organic media used in the same process.[2,3] As a result, great effort has been inspired to this field and effective aqueous phase organic reactions have been documented.[3] Among the aqueous catalytic approaches, asymmetric transfer hydrogenation (ATH) presents several advantages.[4–8] The hydrogen source, sodium formate (HCO_2Na), is water-soluble and produces the volatile co-product, carbon dioxide (CO_2), which facilitates the purification of the reduction products. The transition metal-catalysts are insensitive to water as well as air oxidation, and stable in aqueous media.[5b] Particularly, in the comparison to organic media, the ATH of ketones was performed in water to exhibit significantly higher reactivity,[5] better chemoselectivity,[6] and regioselectivity,[7] even higher enantioselectivity in the presence of surfactants.[3f,6,8a]

Optically active amines are important building blocks for bioactive molecules and natural products, and have also extensively been used as chiral auxiliaries and resolving agents in asymmetric synthesis.[9] Asymmetric reduction of ketimines is the most direct and efficient method for preparation of chiral amines.[9,10] Because ATH possesses an operational simplicity and avoids the handling of hazardous chemicals such as metallic hydrides or molecular hydrogen, recently, the ATH has widely been applied to reduction of ketimines.[11] However, the water-mediated ATH was rarely investigated probably because of the instability of ketimines, especially acyclic ketimines.[4] Previous works indicated that ATH of cyclic ketimines and even ketiminiums was well performed in aqueous media, but the acyclic *N*-sulfonylimines did not work under the same conditions.[8] Since optically active α-arylethylamines are key constituents of chiral drugs and bioactive compounds, such as Rivastigmine, Cinacalcet, and oxazolone derivative (Fig. 1),[9a] we herein like to report the preliminary results on the successful ATH of *N*-sulfonyl arylketimines catalyzed by lipophilic diamine-transition metal-catalysts in the aqueous suspension, which also shows that the recrystallized conditions greatly affect the reactivity of the solid substrates in the heterogeneous aqueous reactions.

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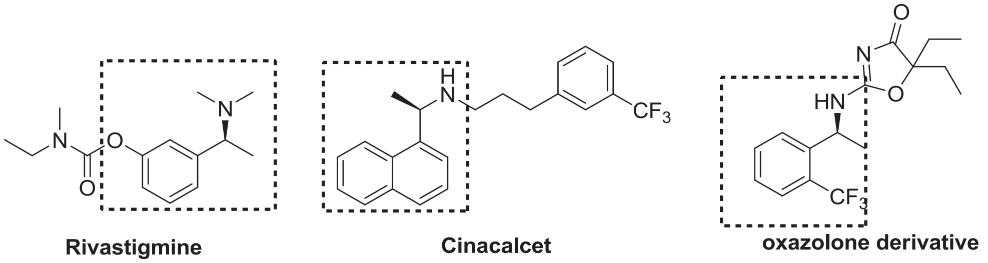
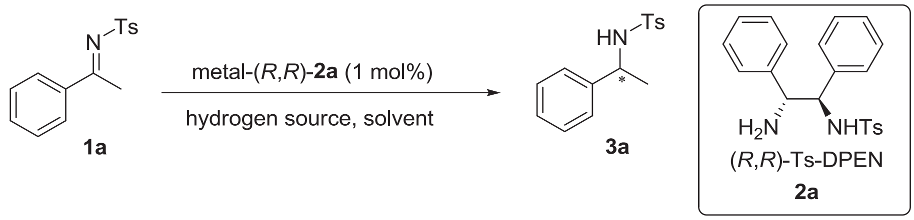


Fig. 1. Structures of pharmaceuticals and bioactive compound with chiral amine moieties.

2. Results and discussion

The previous reports show that *N*-tosyl ketimines are more stable and efficient substrates for highly selective asymmetric hydrogenation in halogenated solvents.[12] However, the development of efficient especially environmental friendly process or catalyzed system for the asymmetric reduction with higher enantioselectivity and more abroad scope of ketimine substrates is still an important research field. Initially, the ATH of *N*-tosyl ketimine **1a** was tried by using 1 mol % of metal-complex prepared via treating (*R*,*R*)-Ts-DPEN (**2a**) and $[RhCl_2(Cp*)]_2$ in situ.[4,13] Table 1 shows that the reactivities and enantioselectivities significantly depend on reaction media (entries 1–7). Interestingly, although **1a** was well dissolved in the common organic solvents, the best yield (98.7%) and enantioselectivity (96.5% ee) were obtained with solid suspensions of **1a** in water (Fig. 2) by using water-soluble HCO_2Na as a hydrogen source after 1 h at 40 °C (entry 7).[14] Vigorous stirring promotes the reactions (entry 8 vs entries 9 and 10), most likely by increasing the area of surface contact between the solid particles and aqueous phases. However, the reaction rate obviously decreased under sonication conditions (entry 11).[14a] The results suggest that the reaction proceeds at the interface between the solid substrates and water in other words 'on water'. Although solid **1a** and Rh-**2a** catalyst produced in situ are only sparingly soluble in water (Fig. 2),[5b,13] the hydrophobic interactions and trans-phase hydrogen-bonding might contribute to accelerate the reactivity.[2c,3b,e] Various types of transition metal complexes were also investigated as catalyst precursors (entries 12–14). Excellent yields were obtained with both $[RhCl_2(Cp*)]_2$ and $[IrCl_2(Cp*)]_2$ as the precursors after 5 h, but slightly poor enantioselectivity was observed with $[IrCl_2(Cp*)]_2$. However, poor yield and low ee value were provided by using $[RuCl_2(p\text{-cymene})]_2$ as a metal precursor, which is obviously different to the results of the imines catalyzed by the water-soluble ligands.[8a,b] Decreasing the reaction temperature

Table 1
Scanning of different solvent, metal precursor, and stirring speed[a]



Entry	Solvent[b]	Metal complex	*T* (°C)	*t* (h)	Yield[c] (%)	ee (%)
1	CH_2Cl_2	$[RhCl_2(Cp*)]_2$	40	1	Trace	n.d.[d]
2	CH_3CN	$[RhCl_2(Cp*)]_2$	40	1	Trace	n.d.
3	MeOH	$[RhCl_2(Cp*)]_2$	40	1	44.6	82.2
4	EtOH	$[RhCl_2(Cp*)]_2$	40	1	47.3	83.6
5	THF	$[RhCl_2(Cp*)]_2$	40	1	83.5	90.1
6	EtOAc	$[RhCl_2(Cp*)]_2$	40	1	91.4	94.2
7	H_2O	$[RhCl_2(Cp*)]_2$	40	1	98.7	96.5
8	H_2O	$[RhCl_2(Cp*)]_2$	40	0.5	96.7	96.4
9[e]	H_2O	$[RhCl_2(Cp*)]_2$	40	0.5	35.4	96.6
10[f]	H_2O	$[RhCl_2(Cp*)]_2$	40	0.5	29.1	96.6
11[g]	H_2O	$[RhCl_2(Cp*)]_2$	40	1	17.2	n.d.
12	H_2O	$[RhCl_2(Cp*)]_2$	40	5	99.1	96.9
13	H_2O	$[IrCl_2(Cp*)]_2$	40	5	99.0	94.3
14	H_2O	$[RuCl_2(p\text{-cymene})]_2$	40	5	21.8	50.8
15	H_2O	$[RhCl_2(Cp*)]_2$	28	27	57.1	97.6
16	H_2O	$[IrCl_2(Cp*)]_2$	28	27	30.3	95.8
17[h]	H_2O	$[RhCl_2(Cp*)]_2$	40	5	82.6	95.2

[a] The reaction in organic media was carried out in 1 mL of solvent under argon atmosphere using 0.4 mmol **1a**. [Rh-(*R*,*R*)-**2a**]/[**1a**]=1:100 and 0.2 mL of a mixture of formic acid and triethyl amine (TEAF, v/v=5:2) as hydrogen source; the reaction in water was carried out in 1 mL of H_2O under argon atmosphere using 0.4 mmol **1a**. [M-(*R*,*R*)-**2a**]/[**1a**]/[HCO_2Na]=1:100:750; stirring speed is 1200 rpm.

[b] Organic solvent was dried before use.

[c] Isolated yield.

[d] n.d.=not detected.

[e] Stirring speed is 700 rpm.

[f] Stirring speed is 300 rpm.

[g] Under sonication conditions.

[h] The reaction was carried out in 1 mL of H_2O under argon atmosphere using 0.8 mmol **1a**. [M-(*R*,*R*)-**2a**]/[**1a**]/[HCO_2Na]=1:200:1500.