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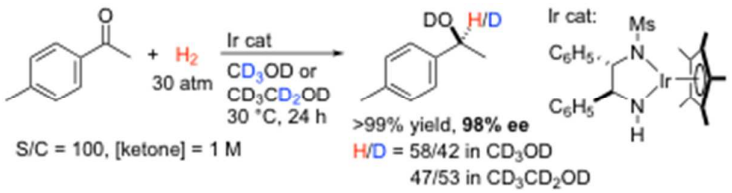

Asymmetric ketone hydrogenation with bifunctional amidoiridium complexes in methanol or ethanol proceeds competitively with asymmetric transfer hydrogenation, in which the pressurised hydrogen can suppress involuntary racemisation of the alcoholic product.

Graphical Abstract

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Advantageous asymmetric ketone reduction with competitive hydrogenation/transfer hydrogenation system using chiral bifunctional iridium catalysts†

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Hydrogenation of aromatic ketones with chiral bifunctional amidoiridium complexes proceeds in preference to transfer hydrogenation in methanol, in which the pressurised hydrogen can suppress involuntary racemisation of the alcoholic product, leading to enhanced enantioselectivity.

Asymmetric reduction of ketones to chiral alcohols is an established and extensively utilised transformation in organic synthesis.[1] Noyori, Ikariya and co-workers have developed a series of well-defined metal/NH bifunctional Ru(η^6-arene) catalysts bearing Tsdpen [Tsdpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] (**1**), for the asymmetric transfer hydrogenation (ATH) of aromatic and propargylic ketones using 2-propanol[2] or formic acid–triethylamine (5:2)[3] as a reaction medium and a hydrogen source (Scheme 1). Analogous Cp*M-Tsdpen and -Tscydn complexes [Cp* = η^5-1,2,3,4,5-pentamethylcyclopentadienyl; M = Rh, Ir; Tscydn = *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine][4] have also been demonstrated to catalyse the ATH of aromatic ketones with 2-propanol, while these complexes were less effective for asymmetric H_2-hydrogenation (AH) of the unsaturated substrates in aprotic solvents. In contrast, some cationic amine equivalents, Ru(OTf)(Tsdpen)(η^6-*p*-cymene), $[Cp^*Rh(Tsdpen)]^+$ and $[Cp^*Ir(Tscydn)(CH_3CN)]^+$, which can be synthesised by treatment of the amido complex with a stoichiometric amount of TfOH or by a chloro(amine) catalyst precursor with silver salts, are found to be highly effective for the AH of either ketones or imines.[5-8] A related Cp*RuCl(cod)/diamine/KOH catalyst, which is isoelectronic to **1** but inert to transfer hydrogenation from 2-propanol, is highly effective for the hydrogenation of ketones in alcohols.[9] In this reaction, the alcoholic solvents are proposed to participate in the H_2 activation through the formation of a hydrogen-bonding network (Scheme 2).[10,11]

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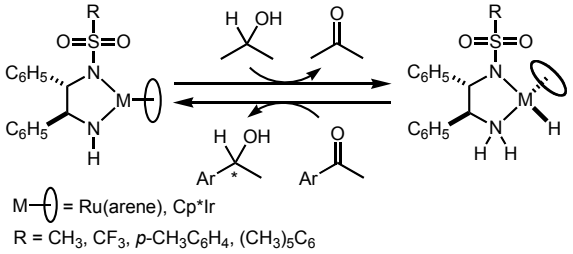
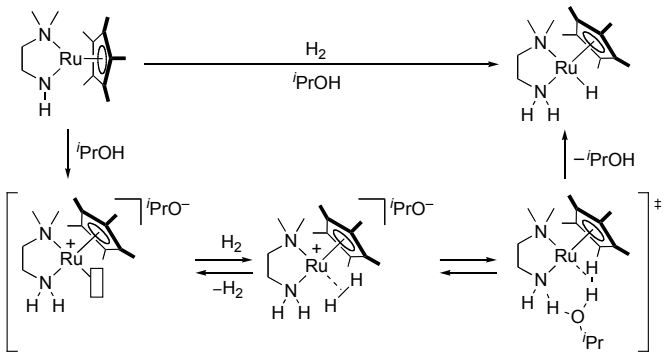


Scheme 1. Hydrogen transfer from alcohols to ketones based on interconversion between amido and hydrido(amine) complexes.



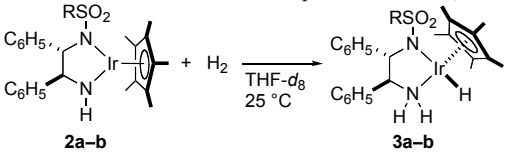
Scheme 2. Heterolysis of molecular hydrogen by cationic amine species.

Herein, we disclose that the catalytic AH of ketones with Cp*Ir[(*S*,*S*)-RSO_2dpen] [RSO_2 = Ms (CH_3SO_2): **2a**, Ts: **2b**] is accelerated by the support of methanol or ethanol without any modification of the amidoiridium complexes. Furthermore, it was experimentally demonstrated that the AH conditions can overcome the intrinsic reversibility of the competitive hydrogen transfer reaction between ketone substrates and alcohol products, leading to higher enantioselectivities rather than the products obtained by ATH.

Our initial efforts concentrated on the stoichiometric reaction of amidoiridium complexes **2a**–**b** with H_2 as shown in Table 1. As mentioned in above, **2b** bearing (*S*,*S*)-TsDPEN ligand did not readily

react with atmospheric pressure of H_2 in aprotic THF (entry 1), and hydridoiridium complexes **3a** and **3b** were formed in yield of 37% and 20% respectively, even under pressurised hydrogen (30 atm) after 6–7 h (entries 2 and 3).

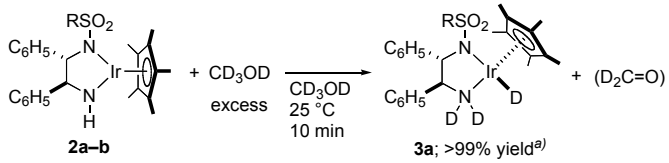
Table 1. Reaction of amidoiridium complexes **2** and H_2.



entry	Ir complex	conc, M	H_2, atm	time, h	% yield[a]
1[b]	**2b**	0.02	1	1	n.r.
2	**2b**	0.03	30	7	20
3	**2a**	0.03	30	6	37

[a] Determined by ^{1}H NMR analysis. [b] n.r. = no reaction.

On the other hand, treatment of amidoiridium complexes **2a** and **2b** in excess CD_3OD provided the corresponding deuterated hydridoiridium complexes, **3a** and **3b**, in excellent yields within 10 min (Scheme 3). In the ^{2}H NMR spectra, the total integral intensity of signals attributed to the coordinating amine on **3a** or **3b** formed is almost two times as much as that of the deuterido ligand, indicating that both amine protons are rapidly exchanged with the OD group of the CD_3OD solvent. The deuterido ligand was exclusively derived from CD_3OD, but unfortunately, the resulting dehydrogenated formaldehyde (CD_2O) was not detected in the methanolic reaction mixtures by NMR spectroscopy, possibly due to formation of hemiacetal species including oligomers.[12]

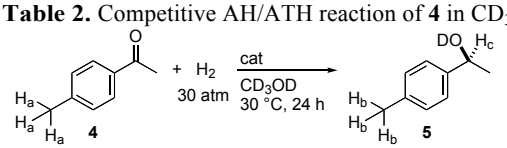


a) Determined by ^{1}H NMR analysis.

Scheme 3. Deuterium transfer from methanol-d_4 to amidoiridium **2**.

Although the amido complexes **2** are highly susceptible to the hydrogen transfer from methanol, it was anticipated that alcoholic solvents could assist the H_2 heterolysis with **2** in similar to the above-mentioned mechanism in Scheme 2, and would operate in favour of catalytic AH without any modification of catalyst structure. In order to evaluate the relative rate of H_2-hydrogenation and transfer hydrogenation using methanol, deuterium labelling reactions of 4'-methylacetophenone (**4**) catalysed by the amidoiridium complexes **2** with a substrate/catalyst molar ratio (S/C) of 100 were conducted in CD_3OD (1 M) under hydrogen pressure (30 atm) at 30 °C. The conversion of the substrate **4** and yield of the alcohols product, 1-(4'-methylphenyl)ethanol (**5**) were determined based on signals of the methyl protons (H_a and H_b) on the aromatic ring of **4** and **5** (2.37 ppm and 2.28 ppm in CD_3OD, respectively) in ^{1}H NMR spectra of the reaction mixture containing triphenylmethane as an internal standard. The deuterium content at the methine hydrogen (H_c) in the product **5** was confirmed by comparing the integral intensity, which enables to discriminate the H_c atoms delivered from CD_3OD and H_2. As summarised in Table 2, when **2a** was used as the catalyst (entry 1), **5** was obtained in almost quantitative yield (>99%) with 98% ee (*S*). In this reaction, the %D value at H_c of **5** was 42%, indicating that 58% of the ketone **4** was reduced via the AH in preference to the ATH from CD_3OD. The reaction conducted in CH_3OD gave **5** without noticeable deuterium incorporation into H_C (entry 2). Consequently, it assures that the AH/ATH estimation under these conditions is not influenced by a potent reversible exchange between the alcoholic proton with the iridium hydride species. The reduction rate dramatically changes depending on the sulfonyl groups on the DPEN ligand of the bifunctional catalysts. The reaction using the amido complex **2b** with a Ts substituent gave **5** in 60% yield with 98% ee (*S*) under the identical reaction conditions (entry 3), whereas **2c** having a bulky pentamethylbenzenesulfonyl group proved to be catalytically less active for the reduction (entry 4). The moderate H_c-deuteration (48% D) in the Tsdpen-Ir system also corroborates the AH in conjunction with the ATH.

Table 2. Competitive AH/ATH reaction of **4** in CD_3OD with **2a-c**.



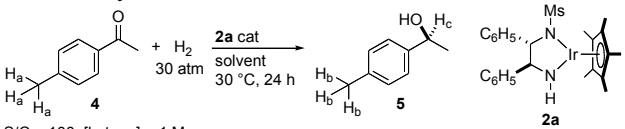
S/C = 100, [ketone] = 1 M

entry	cat	% conv[a]	% yield[a]	% ee[b]	H/D at H_c
1	**2a**	>99(H_a)	>99(H_b)	98	58/42
2[c]	**2a**	99(H_a)	99(H_b)	98	>99/–
3	**2b**	66(H_a)	60(H_b)	98	52/48
4[d]	**2c**	<5(H_a)	<5(H_b)	n.d.	n.d.

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis using a Chiralcel OD-H column. [c] CH_3OD was used as solvent. [d] n.d. = not determined.

When the ATH reaction of **4** using the effective bifunctional catalyst **2a** was performed in CH_3OH under argon atmosphere under otherwise identical conditions, the chiral alcohol **5** was produced in lower yield and enantioselectivity of 85% and 90% ee, compared to the outcome of the AH/ATH reaction. Elongation of the reaction time to 72 h to complete consumption of **4** resulted in 5% loss in optical purity of **5** (entries 1 and 2 of Table 3), because the reversibility in hydrogen transfer between alcohols and ketones is known to deteriorate the enantioselectivity as the reaction time passes. Notably, the simultaneous AH and ATH system holds excellent levels of 97-98% ee during 3-24 h reactions (entries 3–5), suggesting that the pressurised H_2 would make the ATH pathway irreversible. In fact, the deuterium content of 32% at the H_c of **5** after the 3-h reaction was slightly increased to 40% after 6 h, and a further H/D exchange was mostly hampered under the AH conditions. In the ATH in methanol, formaldehyde is generated and can act as the hydrogen acceptor in the reverse hydrogen transfer from the product chiral alcohol; however, the AH reaction will lead to complete consumption of the aldehyde. Therefore, hydrogen pressure is important to maintain the excellent optical purity of the product.

Table 3. Asymmetric reduction of **4** with **2a**.



S/C = 100, [ketone] = 1 M

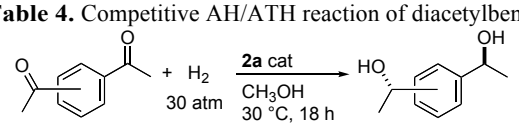
entry	solvent	time, h	% conv[a]	% yield[a]	% ee[b]	H/D at H_c
1[c]	CH_3OH	24	84	85	90	—
2[c]	CH_3OH	72	97	>99	85	—
3	CD_3OD	3	57(H_a)	57(H_b)	97	68/32
4	CD_3OD	6	84(H_a)	78(H_b)	98	60/40
5	CD_3OD	24	>99(H_a)	>99(H_b)	98	58/42
6	C_2D_5OD	24	>99(H_a)	>99(H_b)	98	47/53
7	IPA-d_8	24	56(H_a)	65(H_b)	98	0/100
8[d]	THF	24	11	8	82	—

[a] Determined by ^{1}H NMR analysis and GC analyses. [b] Determined by HPLC analysis using a Chiralcel OD-H column. [c] ATH reaction without H_2. [d] Acetophenone was used as substrate.

The ATH/AH reaction of **4** also proceeded in ethanol-d_6 to give **5** in almost quantitative yield with 98% ee in similar to the reaction in CD_3OD, while increase of the H/D ratio at H_c was observed as a result of enhancement of the ATH from the alcoholic solvent (entry 6). On the contrary, the AH reaction was not promoted in 2-propanol-d_8 to give **5** by net ATH in 65% yield and with 98% ee (*S*) (entry 7). According to the H_2 heterolysis via an ion-pair intermediate composed of a cationic amine complex and an alkoxide counter anion depicted in Scheme 2, it may be more difficult to activate molecular hydrogen in less acidic 2-propanol (pK_a = 17.1) than methanol (pK_a = 15.2) or ethanol (pK_a = 15.9). Actually, hydrogenation of acetophenone was unsuccessful in aprotic THF in the presence of H_2 (30 atm), affording 1-phenylethanol in yield of 8% (entry 8).

The beneficial feature of this hydrogenation guided by methanol was successfully verified by the reaction of diacetylbenzenes, for which few ATH or AH catalysts have been reported.[13] As shown in Table 4, 1,4-diacetylbenzene was almost completely reduced to the corresponding (*S*,*S*)-diol with an excellent enantioselectivity of 99.7% ee and a *dl*/*meso* ratio of 96/4 (entry 1), whereas the ATH in methanol resulted in a moderate conversion of 43%, affording a small amount (1% yield) of the diol in addition to a mono-alcohol product, (*S*)-1-acetyl-4-(1-hydroxyethyl)benzene (41% yield, 84% ee). The AT/ATH reaction of 1,3-diacetylbenzene also furnished (*S*,*S*)-1,3-bis(1-hydroxyethyl)benzene with 99.5% ee, as well (entry 3).

Table 4. Competitive AH/ATH reaction of diacetylbenzenes.



S/C = 100, [ketone] = 1 M (*S*,*S*)-diol

entry	substrate	% conv[a]	% yield (diol)[a]	% ee[b]	*dl*/*meso*[b]
1	1,4-diacetylbenzene	100	>99	99.7	96/4
2[c]	1,4-diacetylbenzene	43	1	—	—
3	1,3-diacetylbenzene	100	99	99.5	95/5

[a] Determined by ^{1}H NMR analysis.
[b] Determined by GC analysis using a CP-Chirasil-Dex CB column.
[c] ATH reaction in a methanol solution (0.5 M) without H_2.

In conclusion, the formation of bifunctional hydridoiridium complexes via heterolytic cleavage of H_2 using amidoiridium **2** become competitive to hydrogen transfer from alcoholic hydrogen donors by employment of primary alcohols as the solvent. The simultaneous hydrogenation favourably influences the outcome of stereoinduction, owing to overcome undesired decrease in optical purity of the chiral alcohol products arising from the inherent reversibility of the hydrogen transfer reaction between ketones and alcohols. In comparison with the original ATH, this AH/ATH system is advantageous to accelerate the ketone reduction with maintaining the excellent enantiomer discrimination ability of the bifunctional Ir catalysts without any modification of the molecular structure.

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