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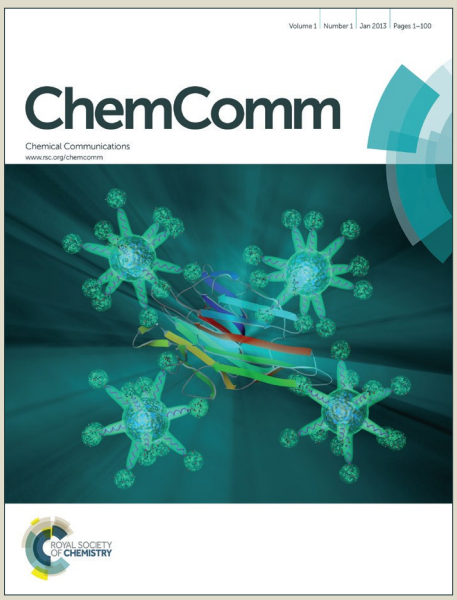

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# Chiral-at-Metal Iridium Complex for Efficient Enantioselective Transfer Hydrogenation of Ketones

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**A bis-cyclometalated iridium(III) complex with metal-centered chirality catalyzes the enantioselective transfer hydrogenation of ketones with high enantioselectivities at low catalyst loadings down to 0.002 mol%. Importantly, the rate of catalysis and enantioselectivity are markedly improved in the presence of a pyrazole co-ligand. The reaction is proposed to proceed *via* an iridium-hydride intermediate exploiting metal-ligand cooperativity (bifunctional catalysis).**

Transition metal catalyzed asymmetric transfer hydrogenation (ATH) has developed into a popular method for the generation of non-racemic chiral alcohols and amines using isopropanol, formic acid/triethylamine or sodium formate as convenient and inexpensive hydrogen sources.[1] Since Noyori's seminal discovery of highly enantioselective ATH catalysts based on ruthenium(II) half sandwich complexes containing monotosylated 1,2-diamines,[2] transition metals such as Ru(II),[3] Os(II),[4] Ir(III),[5] Rh(III),[6] and Fe(II)[7] have been combined with a large variety of different chiral ligands to achieve high turnover numbers (TON) and turnover frequencies (TOF) for different substrate classes.[8] Here we report a unique catalyst that relies on metal-centered chirality using exclusively achiral ligands.[9]

We recently developed a novel class of chiral Lewis acid catalysts based on octahedral chiral-only-at-metal iridium(III) and rhodium(III) complexes, in which the octahedral metal center is coordinated irreversibly by two cyclometalating bidentate ligands in a propeller-type fashion, complemented by two exchange-labile acetonitriles.[10-17] In these catalysts, metal-centered chirality (metal centrochirality) is the only source of chirality. We were wondering if such complexes are suitable for catalyzing ATH and we used the reduction of acetophenone as our initial model reaction (**1a**→**2a**, Figure 1).

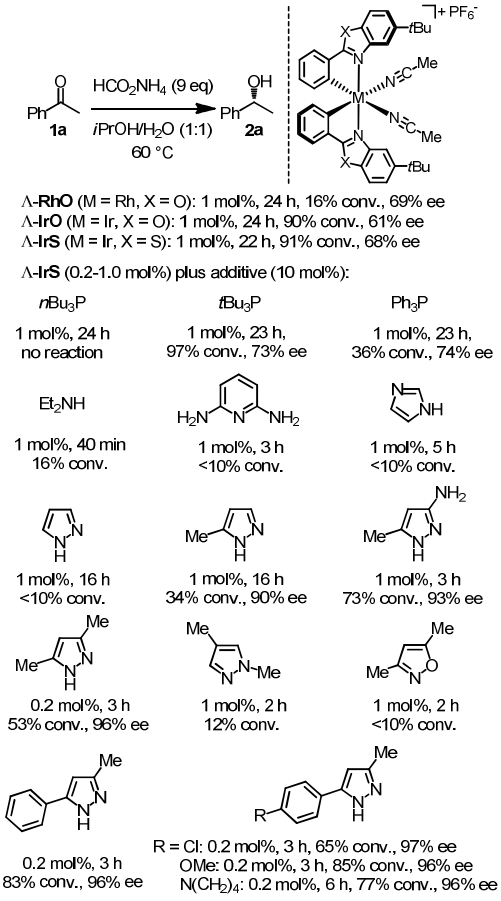


**Figure 1** Initial experiments and screening of ligand additives. Conversion determined by $^1$H-NMR and enantioselectivity by HPLC on a chiral stationary phase.

Using ammonium formate as the hydrogen source, the rhodium complex Λ-**RhO** (1 mol%) catalyzed the reduction of acetophenone only sluggishly, providing just 16% conversion and 69% ee after 24 hours at room temperature, whereas the

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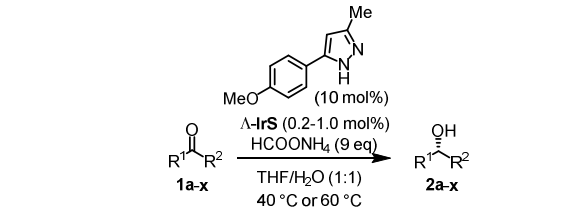
higher congener Λ-**IrO** (1 mol%) gave better results with 90% conversion after 24 hours and 61% ee. Replacing the benzoxazole ligands (Λ-**IrO**) against benzothiazole (Λ-**IrS**) further improved the outcome reaching 91% conversion after 22 hours with 68% ee. We therefore chose Λ-**IrS** as the catalyst of choice and next investigated the effect of additional monodentate ligands on the catalysis. The results are shown in Figure 1. Whereas some ligands such as $n$Bu$_3$P, 2,6-diaminopyridine or imidazole suppressed the catalytic activity, others such as $t$Bu$_3$P resulted in a slight improvement of the enantioselectivity. To our delight, 3,5-dimethylpyrazole markedly improved the catalytic activity and enantioselectivity. With a reduced catalyst loading of just 0.2 mol%, 3 hours reaction time resulted in a conversion of 53% with 96% ee. Replacing the methly group at the 5-position with a phenyl moiety further improved the results with the best compromise out of reaction rate and enantioselectivity achieved with 5-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole.

We used the combination of Λ-**IrS** (0.2-1.0 mol%) and the best pyrazole additive (10 mol%) for investigating the substrate scope (**1a**-**x**) under optimized conditions in THF/$H_2O$ (1:1) as the solvent. Figure 2 reveals that the ATH reaction of acetophenones with electron donating or withdrawing substitutents within the phenyl moiety provided both high yields and good enantioselectivities (products **2a**-**d**,**f**,**g**) with an exception of the *ortho*-methyl substituted substrate (product **2e**, 51% ee). Typically, electron withdrawing groups were slightly less beneficial with regard to enantioselectivity, which might be due to some contribution from uncatalyzed background reaction. Other aromatic ketones containing a naphthyl moiety (product **2h**), heteroaromatic ring (products **2i**-**n**), larger aliphatic groups (products **2o**-**q**), or an additional ester functionality (product **2r**), as well as a cyclic ketone (product **2s**) were all well converted. Diaryl ketones also provided satisfactory results (products **2t**,**u**). As for dialkyl ketones bearing two primary alkyl chains, for example affording the alcohols **2v** and **2w**, high yields (90-94%) while low ee values (9% and 30% ee, respectively) were achieved. However, a substrate with one bulky secondary alkyl substituent afforded the desired alcohol **2x** with 93% yield and 94% ee within 15 hours, suggesting that aliphatic ketones could also work nicely for selected cases. In addition, it is worth to mention that the reaction can be scaled up. For example, 1.0 g of phenyl(o-tolyl)methanone produced 0.99 g of its corresponding alcohol **2t** (yield 99%) with 97% ee in presence of 0.5 mol% catalyst.[‡]

Next, we chose 2-acetyl benzothiophene for testing catalytic performance of the Λ-**IrS**/monodentate pyrazole system at lower catalyst loadings (**1n**→**2n**). As illustrated in Table 1, the catalyst loading could be reduced to 0.005 mol% (S/C = 20000) while still keeping a satisfactory reaction time of 108 hours for complete conversion at 60 °C without affecting the enantioselectivity (entries 1–5). A further reduction to 0.002 mol % catalyst led to a slight drop in enantioselectivity value (96.6% ee) while a significantly lower reaction rate prevented full conversion (entry 6).



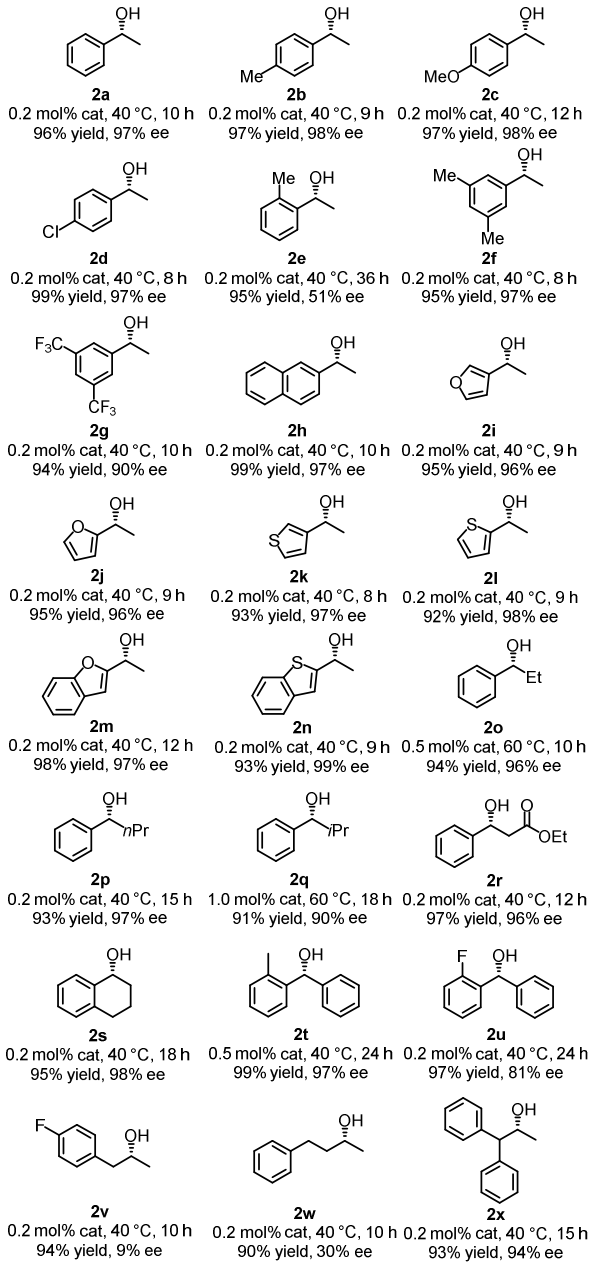




**Figure 2** Substrate scope with prochiral ketones.

Mechanistically, we propose that the precatalyst Λ-**IrS** bearing labile acetonitriles undergoes fast ligand exchange with one pyrazole molecule, followed by reaction with ammonium formate to generate an active iridium hydride species. With assistance of the ancillary pyrazole ligand, the subsequent concerted transfer of a

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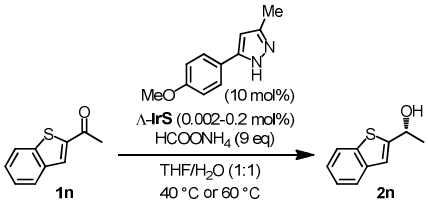
hydride to the carbonyl carbon and a proton to the carbonyl oxygen leads to formation of the chiral secondary alcohol. The effective asymmetric induction can be explained by less steric hindrance in the favored transition state as well as additional π-π stacking between the aromatic ring of the substrate and one cyclometalating benzothiazoline moiety of the iridium complex (Figure 3, left side). The high catalytic efficiency is in parts attributed to the rigid structure of the catalyst and intermediate limiting the degree of conformational flexibility, thereby providing entropic advantages during catalysis. The mechanism is consistent with an observed *R*-configuration of the formed chiral alcohol assigned by comparison of optical rotations with published examples.[8e,18] Additionally, the importance of the ancillary pyrazole ligand with the crucial role of the N-H group is supported by the sluggish results achieved with closely related additive ligands which lack this N-H, such as 1,4-dimethyl-1H-pyrazole or 3,5-dimethylisoxazole.[19] (Figure 1). A crystal structure of 5-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole coordinated to the bis-cyclometalated iridium complex confirms that the pyrazole prefers a conformation in which the N-H group is in a perfect position for the proposed bifunctional catalysis.[20]

**Table 1** Asymmetric transfer hydrogenation with 2-acetyl benzothiophene[a]




| Entry | cat. loading | T (°C) | *t* (h) | conv. (%)[d] | ee (%)[e] |
|---|---|---|---|---|---|
| 1 | 0.2 mol% | 40 | 9 | quant. | 98.7 |
| 2 | 0.05 mol% | 40 | 30 | quant. | 98.7 |
| 3 | 0.01 mol% | 40 | 144 | quant. | 98.7 |
| 4 | 0.01 mol% | 60 | 48 | quant. | 98.4 |
| 5 | 0.005 mol% | 60 | 108 | quant. | 98.4 |
| 6[d] | 0.002 mol% | 60 | 120 (240) | 51 (56) | 96.6 (96.6) |

[a]Reaction conditions: A mixture of Λ-**IrS** (0.002-0.2 mol%), 5-(4-methoxyphenyl)-3-methyl-*1H*-pyrazole (0.066 mmol), and $HCOONH_4$ (6.0 mmol) in THF/$H_2O$ (1:1) (0.67 mL) was stirred at room temperature for 10 min before the substrate 2-acetyl benzothiophene (0.66 mmol) was added and the solution stirred at 40 or 60 °C for the indicated time.
[b]Conversion determined by $^1$H-NMR.
[c]Enantioselectivity by HPLC on a chiral stationary phase.
[d]Values in bracket for a reaction time of 240 hours.

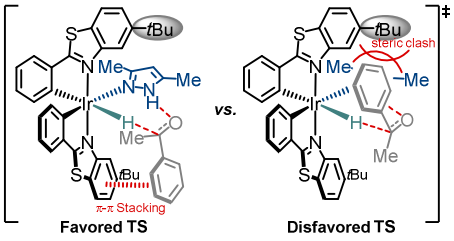



**Figure 3** Proposed transition states through the association of the substrate with a pyrazole-coordinated iridium hydride intermediate explaining the observed enantioselectivities.

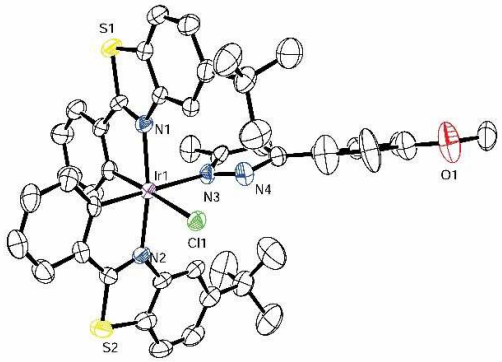



**Figure 4** Crystal structure of an iridium chlorido complex with coordinated pyrazole ligand. ORTEP drawings with 50% thermal ellipsoids. The complex was crystallized as a racemate but only the Λ-enantiomer is shown.

In conclusion, we here reported a highly efficient asymmetric transfer hydrogenation for ketones catalyzed by a bis-cyclometalated chiral-at-metal iridium(III) complex in the presence of an additional pyrazole ligand. The reaction is proposed to proceed through an iridium-hydride intermediate exploiting metal-ligand cooperativity involving the coordinated pyrazole ligand. A variety of aryl ketones and even one aliphatic ketone are well tolerated in the ATH reaction by affording the secondary alcohols with good to excellent enantioselectivities at catalyst loadings down to 0.002 mol%. Applications to other substrate classes such as imines are ongoing in our laboratory.

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## Notes and references

**‡Catalysis on gram-scale:** To a biphasic solution of 5-(4-methoxyphenyl)-3-methyl-1*H*-pyrazole (95.9 mg, 0.51 mmol) and $HCOONH_4$ (2.89 g, 45.9 mmol) in THF/$H_2O$ (2.57 mL/2.57 mL) was added the metal catalyst Λ-**IrS** (24.3 mg, 0.026 mmol) in a brown glass vial. The mixture was stirred for 10 min at room temperature, then phenyl(*o*-tolyl)methanone (**1t**, 1.00 g, 5.10 mmol) was added. The reaction solution was stirred at 40 °C for 30 h, cooled down to room temperature and then dried under high vacuum. The residue was purified by flash chromatography on silica gel (*n*-hexane/dichloromethane = 1:1 to 1:2) to afford product **2t** as a yellow solid (0.999 g, 5.07 mmol, yield: 99%). Enantiomeric excess of 97% ee was established by HPLC analysis (Chiralpak OJ column, 250 x 4.6 mm, absorbance at 220 nm, *n*-hexane/isopropanol = 95:5, flow rate: 1.0 mL/min, 25 °C, $t_r$(minor) = 27.2 min, $t_r$(major) = 30.8 min). $[\alpha]^{20}_D$ = +6.8 (c 1.0, $CHCl_3$).

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