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Asymmetric Catalysis with an Inert Chiral-at-Metal Iridium Complex

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Supporting Information

ABSTRACT: The development of a chiral-at-metal iridium(III) complex for the highly efficient catalytic asymmetric transfer hydrogenation of β,β'-disubstituted nitroalkenes is reported. Catalysis by this inert, rigid metal complex does not involve any direct metal coordination but operates exclusively through weak interactions with functional groups properly arranged in the ligand sphere of the iridium complex. Although the iridium complex relies only on the formation of three hydrogen bonds, it exceeds the performance of most organocatalysts with respect to enantiomeric excess (up to 99% ee) and catalyst loading (down to 0.1 mol %). This work hints at an advantage of structurally complicated rigid scaffolds for non-covalent catalysis, which especially relies on conformationally constrained cooperative interactions between the catalyst and substrates.

The growing impact of asymmetric catalysis in chemistry is driven by an increasing demand for the economical synthesis of enantiomerically pure chiral compounds to be used as drugs, agricultural chemicals, flavors, fragrances, and components of materials.[1,2] Over the past decade, organocatalysis has emerged as a new branch of enantioselective synthesis.[3] In one general mode of activation, substrate binding and activation is solely achieved via multiple, concerted non-covalent interactions, such as hydrogen bonds.[4] Despite the attractiveness of this concept, the catalytic rate acceleration for such reactions is often only modest, thus requiring high catalyst loadings. This can be traced back to the fact that attractive non-covalent interactions are considerably weaker than coordinative or covalent bonds and thus are more affected by dynamic and entropic effects. The performance of such non-covalent catalysts therefore crucially relies on the proper relative and absolute arrangement of key activating functional groups in the three-dimensional space, and we envisioned that octahedral metal complexes may serve as powerful structural templates for the design of such non-covalent "organocatalysts".[5−12] Octahedral stereocenters permit the straightforward generation of compounds with high shape and stereochemical complexity and furthermore simplify the design of defined globular and rigid structures because the molecular geometries are basically constructed from a common center with chelating ligands limiting the degree of conformational flexibility.[13] Here we demonstrate how this sophisticated octahedral stereochemistry can be exploited for the tailored design of a highly efficient low-loading asymmetric non-covalent catalyst.[7]

Inspired by bifunctional double hydrogen-bond donor asymmetric organocatalysts such as the thiourea shown in Figure 1, in which the thiourea activates an electrophile while an additional functional group serves as a hydrogen-bond acceptor to activate an incoming nucleophile, we chose the substitutionally inert bis-cyclometalated iridium(III) complex Λ-**Ir1** (Figure 2) as the starting point for our study.[14,15] In this design, a coordinated 5-amino-3-(2-pyridyl)-1*H*-pyrazole acts as a double hydrogen-bond donor to a nitroalkene, whereas a hydroxymethyl substituent on a benzoxazole ligand serves as a hydrogen-bond acceptor for the incoming nucleophile.[16]

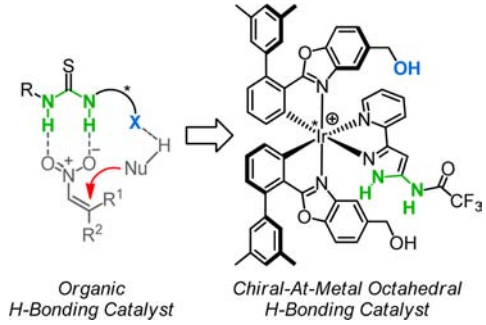
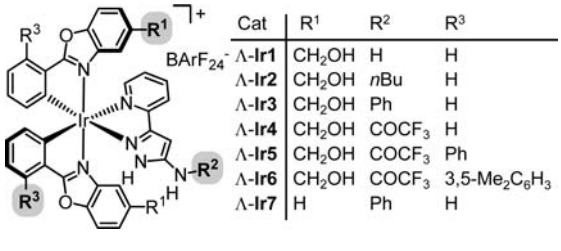


Figure 1. Bifunctional hydrogen-bonding asymmetric organocatalysis as inspiration for a chiral-at-metal iridium catalyst. Stereogenic centers are indicated with asterisks.



Cat	R^1	R^2	R^3
Λ-**Ir1**	CH_2OH	H	H
Λ-**Ir2**	CH_2OH	*n*Bu	H
Λ-**Ir3**	CH_2OH	Ph	H
Λ-**Ir4**	CH_2OH	$COCF_3$	H
Λ-**Ir5**	CH_2OH	$COCF_3$	Ph
Λ-**Ir6**	CH_2OH	$COCF_3$	3,5-$Me_2C_6H_3$
Λ-**Ir7**	H	Ph	H

Figure 2. Chiral-at-metal iridium complexes investigated for asymmetric hydrogen-bonding catalysis. See the Supporting Information for the synthesis of the enantiopure iridium complexes. $BArF_{24}^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

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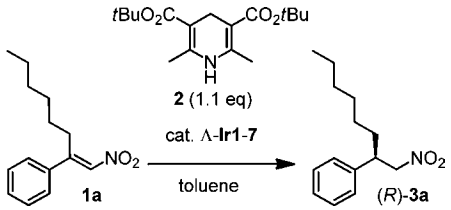
Encouragingly, we found that Λ-**Ir1** catalyzes the asymmetric reduction of β,β′-disubstituted nitroalkene **1a** by Hantzsch ester **2** (1.1 equiv) to afford the nitroalkane (*R*)-**3a**, albeit with modest enantiomeric excess of 63% at a catalyst loading of 20 mol % (Table 1, entry 1).[17−19] However, when we modified the exocyclic primary amine with an *n*-butyl group (Λ-**Ir2**), a phenyl group (Λ-**Ir3**), or a trifluoroacetyl group (Λ-**Ir4**), the ee values increased to 70%, 84%, and 90%, respectively (entries 2−4). The introduction of the trifluoroacetyl group also significantly accelerated the catalysis, presumably because of an increase in the acidity of the amide NH group (entry 4). In the next round of catalyst optimization, we attempted to influence the binding of the nitroalkene substrate by introducing steric constraints at the two R^3 sites in Figure 2. To our delight, Λ-**Ir5** bearing just an additional phenyl substituent at each R^3 site in comparison with Λ-**Ir4**, provided a significant increase in enantiomeric excess and reaction rate (99% ee, with complete conversion within 1 h at room temperature at 20 mol % catalyst loading; entry 5). Reducing the catalyst loading to 1 mol % still afforded the nitroalkane with 98% ee within 20 h at room temperature (entry 6). Finally, the catalytic efficiency was further improved using Λ-**Ir6**, in which each of the phenyl moieties was modified with two methyl groups. At a loading of 1 mol %, Λ-**Ir6** catalyzed the **1a** → (*R*)-**3a** conversion with 99% ee within 14 h at room temperature (entry 7). To summarize this part, the modularity of the metal complex scaffold allowed a rapid, stepwise optimization of the catalysis performance.

Table 1. Development of Inert Chiral-at-Metal Ir(III) Complexes for the Asymmetric Transfer Hydrogenation of Nitroalkene 1a with Hantzsch Ester 2[a]

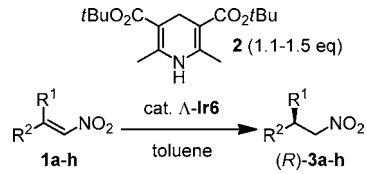


entry	catalyst	loading (mol %)	*t* (h)	conv. (%)[b]	ee (%)[c]
1	Λ-**Ir1**	20	22	92	63
2	Λ-**Ir2**	20	24	82	70
3	Λ-**Ir3**	20	20	94	84
4	Λ-**Ir4**	20	7	96	90
5	Λ-**Ir5**	20	1	100	99
6	Λ-**Ir5**	1	20	96	98
7	Λ-**Ir6**	1	14	94	99
8	Λ-**Ir7**	20	20	<20	0

[a]Reaction conditions: mixtures of **1a** (0.10 mmol), **2** (0.11 mmol), and catalyst (1−20 mol %) in toluene (0.10 mL, 1.0 M) were stirred at room temperature (18−20 °C) under argon. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC analysis.

Next, we tested the scope of catalyst Λ-**Ir6**. Table 2 reveals that a selection of eight β,β′-disubstituted nitroalkenes **1a−h** provided the corresponding reduced nitroalkane products (*R*)-**3a−h** in high yields with excellent enantioselectivities (93−99% ee) at a catalyst loading of just 1 mol % and reaction times of ≤24 h at room temperature (entries 1−8). For practical purposes, it is interesting that the catalyst loading could be reduced even below 1 mol % without much affecting the reached enantioselectivities and yields. For example, at an Λ-**Ir6** catalyst loading of just 0.3 mol %, **1a** was converted to (*R*)-**3a** in 95% yield with 97% ee at room temperature within 3 days. Astonishingly, even at a catalyst loading of 0.1 mol %, a satisfactory yield of 89% with 94% ee was reached. A survey of the literature revealed that with this combination of high enantioselectivity and low catalyst loading, Λ-**Ir6** appears to match or even surpass the best published metal,[20] bio-,[21] and organocatalysts[19b,d] for the asymmetric conjugate reduction of β,β′-disubstituted nitroalkenes.

Table 2. Scope of the Asymmetric Transfer Hydrogenation with Λ-Ir6[a]



entry	R^1, R^2 (substrate)	Λ-**Ir6** loading (mol %)	*t* (h)	yield (%)[b]	ee (%)[c]
1	*n*Hex, Ph (**1a**)	1	18	94	99
2[d]	*n*Pr, Ph (**1b**)	1	24	96	98
3	*i*Pr, Ph (**1c**)	1	24	92	96
4	Me, Ph (**1d**)	1	22	91	95
5	Me, *p*-MePh (**1e**)	1	24	95	95
6	Me, *p*-ClPh (**1f**)	1	24	93	94
7	Me, *m*-ClPh (**1g**)	1	24	91	93
8	Me, 2-naphthyl (**1h**)	1	24	96	96
9	*n*Hex, Ph (**1a**)	0.3	72	95	97
10	*n*Hex, Ph (**1a**)	0.1	96	89	94

[a]Reaction conditions: Mixtures of **1a−h** (0.10 mmol), **2** (0.11 mmol for entries 1−8; 0.15 mmol for entries 9 and 10), and Λ-**Ir6** (0.1−1.0 mol %) in toluene (0.10 mL, 1.0 M) were stirred at room temperature (18−20 °C) under argon. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The reaction was scalable to 1.0 mmol of substrate, providing (*R*)-**3b** in 97% yield with 97.4% ee after 24 h at room temperature (ca. 27 °C).

The performance of the bis-cyclometalated iridium(III) complex Λ-**Ir6** demonstrates that inert octahedral chiral-at-metal complexes are not merely a laboratory curiosity but show great promise for the design of asymmetric catalysts. Since these iridium complexes are substitutionally inert, the observed catalysis must be mediated through the ligand sphere.[22] Interestingly, in our optimized catalyst Λ-**Ir6**, the three bidentate ligands appear to contribute to the efficient catalysis in a cooperative fashion. Figure 3 presents a model of the ternary complex leading to the transition state that is consistent with the observed preference for the formation of the *R*-configured nitroalkane catalyzed by the Λ-configured iridium complex. On the basis of related previous work on the activation of nitroalkenes by thiourea[15,16,19] in addition to mechanistic investigations regarding the role of the OH group in bifunctional thiourea organocatalysts by Paradies and co-workers,[19d] it can be assumed that the amidopyrazole moiety is responsible for activating the nitroalkene by double hydrogen bonding, which increases the electrophilicity of the nitroalkene, while one of the two cyclometalated phenylbenzoxazole ligands places an OH group in the proper position to activate the hydride donor ability of the Hantzsch ester through the formation of a hydrogen bond between the NH group of the Hantzsch ester and a lone pair of the OH group. In fact, complex Λ-**Ir7** derived from Λ-**Ir3** by removal of the OH group does not show any asymmetric induction (Table 1, entry 8), thus confirming the importance of the OH group for the

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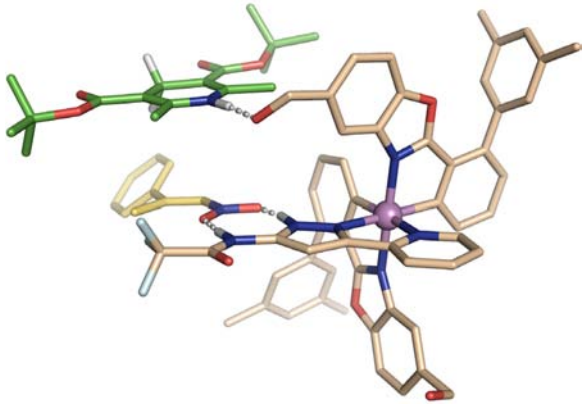

Figure 3. Proposed hydrogen-bonded ternary complex formed by catalyst Λ-**Ir6** (wheat), nitroalkene **1d** (yellow), and Hantzsch ester **2** (green) leading to the transition state. The image was prepared using PyMOL version 1.3 (Schrödinger, LLC).

observed enantioselectivity. Furthermore, the second cyclometalated phenylbenzoxazole orients an aryl substituent in a position that apparently is also important for the catalysis. It is noteworthy that the 3,5-dimethylphenyl substituent in Λ-**Ir6** not only improves the asymmetric induction relative to the analogous complex devoid of this substituent (Λ-**Ir4**) but also speeds up the catalysis by around an order of magnitude. It is curious that a steric group accelerates the catalysis, and we hypothesize that this might be due to stabilization of the proper hydrogen bonding of the nitroalkene substrate by preventing dynamic motion perpendicular to the two formed hydrogen bonds. However, attractive van der Waals interactions between the 3,5-dimethylphenyl substituent of the catalyst and the nitroalkene substrate that would stabilize the major transition state may also play an important role.

In conclusion, we have reported a highly efficient asymmetric catalyst that solely relies on octahedral chirality at the metal.[23] We estimate that the inert iridium complex Λ-**Ir6** accelerates the rate of the asymmetric transfer hydrogenation reaction by ca. 10 000-fold.[24] One can speculate that the rigidity of the octahedral metal complex, in which the conformational freedom is limited by chelate effects, might provide an advantage over the typical more flexible organocatalysts, as the preorganization of the ternary complex must play an important role in lowering the entropic penalty to be paid for the highly organized transition state. We believe that these results demonstrate that the herein-disclosed design based on rigid and inert chiral-at-metal octahedral metal complexes, a class of compounds that has previously been more or less neglected for the design of asymmetric catalysts, will serve as an attractive scaffold for the design of an entire family of highly efficient metal-based non-bonding asymmetric catalysts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, chiral HPLC traces, CD spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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