Communication

Asymmetric Catalysis with Inert Chiral-At-Metal Iridium Complex

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Asymmetric Catalysis with Inert Chiral-At-Metal Iridium Complex

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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 cooperative, weak interactions with functional groups properly arranged in the ligand sphere of the iridium complex. Although the iridium complex only relies 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 towards an advantage of structurally complicated, rigid scaffolds for non-covalent catalysis which especially relies on conformationally constrained, cooperative interactions between 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 noncovalent interactions, such as hydrogen bonds.[4] Despite the attractivity of this concept, the catalytic rate acceleration for such reactions is often only modest, thus requiring high catalyst loadings, which can be traced back to the fact that attractive noncovalent interactions are considerably weaker than coordinative or covalent bonds and thus are more affected by dynamic and entropic effects. The performance of such noncovalent 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 noncovalent "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 molecular geometries are basically constructed from a common center with chelating ligands limiting the degree of conformational flexibility.[13] We here now demonstrate how this sophisticated octahedral stereochemistry can be exploited for the tailored design of a highly efficient low-loading asymmetric noncovalent catalyst.[7]

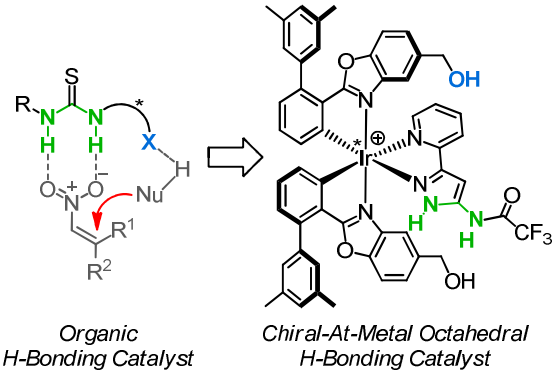
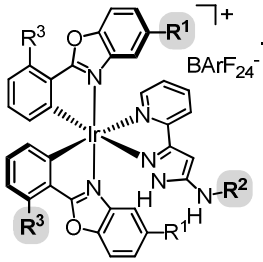


Figure 1. Bifunctional hydrogen bonding asymmetric organocatalysis as inspiration for a chiral-at-metal iridium catalyst. Stereogenic centers are indicated with asterisks.

Inspired by bifunctional double H-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 for activating 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 provides two donor-hydrogen bonds to a nitroalkene, whereas a hydroxymethyl substituent at a benzoxazole ligand serves as a hydrogen bond acceptor for the incoming nucleophile.[16]

Encouragingly, we found that Λ-**Ir1** catalyzes the asymmetric reduction of the β,β'-disubstituted nitroalkene **1a** with the Hantzsch ester **2** (1.1 eq) to afford the nitroalkane (*R*)-**3a**, albeit with modest enantiomeric excess of 63% at 20 mol% catalyst loading (entry 1, Table 1).[17-19] However, when we modified the exocyclic primary

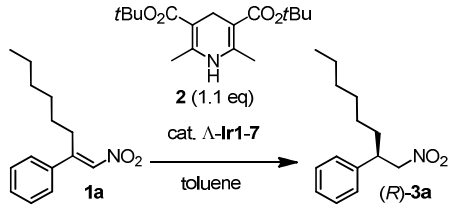
amine with *n*-butyl (Λ-**Ir2**), phenyl (Λ-**Ir3**) or a trifluoroacetyl group (Λ-**Ir4**), the *ee* values increased to 70%, 84% and 90%, respectively (entries 2-4, Table 1). The introduction of the trifluoroacetyl group also significantly accelerated the catalysis, presumably due to an increase in the acidity of the amide NH-group (entry 4, Table 1). In the next round of catalyst optimization, we attempted to influence the binding of the nitroalkene substrate by introducing steric constraints. To our delight, Λ-**Ir5**, in comparison to Λ-**Ir4** just bearing an additional phenyl substituent, provided a significant increase in enantiomeric excess (99% *ee*) and



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 H-bonding catalysis. See Supporting information for the synthesis of the enantiopure iridium complexes. $BArF_{24}^-$ = tetrakis[(3,5-di-trifluoromethyl)phenyl]borate.

Table 1. Development of inert chiral-at-metal Ir(III) complexes for the asymmetric transfer hydrogenation with Hantzsch ester[a]



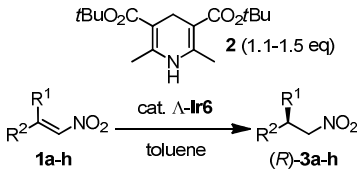
entry	catalyst	amount cat.	*t* (h)	conv. (%)[b]	*ee* (%)[c]
1	Λ-**Ir1**	20 mol%	22	92	63
2	Λ-**Ir2**	20 mol%	24	82	70
3	Λ-**Ir3**	20 mol%	20	94	84
4	Λ-**Ir4**	20 mol%	7	96	90
5	Λ-**Ir5**	20 mol%	1	100	99
6	Λ-**Ir5**	1 mol%	20	96	98
7	Λ-**Ir6**	1 mol%	14	94	99
8	Λ-**Ir7**	20 mol%	20	<20	0

[a] Reaction conditions: Nitroalkene **1a** (0.10 mmol), Hantzsch ester **2** (0.11 mmol) and Λ-**Ir1-7** (1-20 mol%) in toluene (0.10 mL, 1.0 M) were stirred at room temp. (ca. 18-20 °C) under argon. [b] Conversion determined by ^{1}H-NMR. [c] Determined by chiral HPLC analysis.

reaction rate (complete conversion within 1 h at room temperature at 20 mol% catalyst loading) (entry 5, Table 1). Reducing the catalyst loading to 1 mol% still afforded the nitroalkane in 98% *ee* within 20 hours at room temperature. Finally, the catalytic efficiency could be further improved by modifying the phenyl moiety with two methyl groups (Λ-**Ir6**) (entry 6, Table 1). With a loading of 1 mol%, Λ-**Ir6** catalyzes the conversion **1a**→(*R*)-**3a** with 99% *ee* within 14 hours at room temperature (entry 7, Table 1). To summarize this part, the modularity of the metal complex scaffold allowed us a rapid, stepwise optimization of the catalysis performance.

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

Table 2. Scope of the asymmetric transfer hydrogenation with Λ-**Ir6**.[a]



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

[a] Reaction conditions: Nitroalkenes **1a-h** (0.10 mmol), Hantzsch ester **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 temp. (ca. 18-20 °C) under argon. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction is scalable to 1.0 mmol substrate, providing (*R*)-**3b** with 97% yield and 97.4% *ee* after 24 h at room temp. (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 high 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**, all three bidentate ligands appear to contribute to an efficient catalysis in a cooperative fashion. A model of the ternary complex leading to the transition state is presented in Figure 3 and is consistent with the observed preference for the formation of the *R*-configured nitroalkanes catalyzed by the Λ-configured iridium complexes. Based on 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 *et al.*,[19d] it can be assumed that the amidopyrazole moiety is responsible for activating the nitroalkene by double hydrogen bonding and thus increasing the electrophilicity of the nitroalkene, while one of the two cyclometalated phenybenzoxazole ligands places an OH-group in a proper position for activating the hydride donor ability of the Hantzsch ester by forming 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 removing the OH-group, does not show any asymmetric induction (entry 8, Table 1), thus confirming the importance of the OH-group for the observed enantioselectivities. Furthermore, the second cyclometalated phenylbenzoxazole orients an aryl substituent in a position which apparently is also important for the catalysis. It is noteworthy that the 3,5-dimethylphenyl substituent in Λ-**Ir6** does not only improve the asymmetric induction compared 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 catalysis and we hypothesize that this might be due to a stabilization of the proper hydrogen bonding of the nitroalkene substrate, preventing a 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 which would stabilize the major transition state may also play an important role.

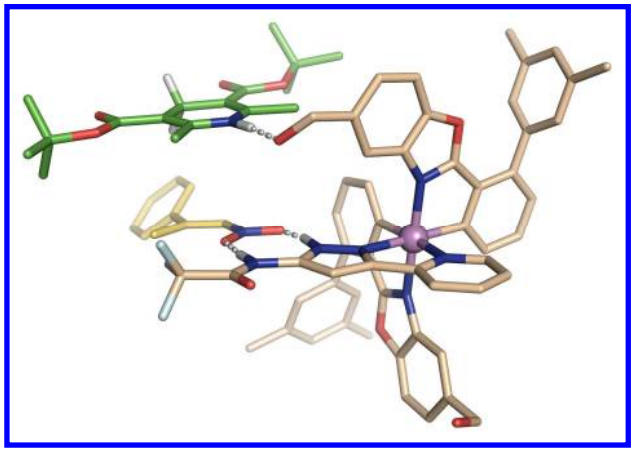


Figure 3. Proposed hydrogen bonded ternary complex out of catalyst Λ-**Ir6** (wheat), nitroalkene **1d** (yellow) and Hantzsch ester **2** (green) leading to the transitions state. Represented with the PyMOL Molecular Graphics System, Version 1.3 Schrödinger, LLC.

In conclusion, we here reported a highly efficient asymmetric catalyst solely relying on octahedral chirality-at-metal.[23] We estimate that the inert iridium complex Λ-**Ir6** accelerates the rate of the asymmetric transfer hydrogenation reaction by around 10,000-fold.[24] One can speculate that the rigidity of the octahedral metal complex, in which conformational freedom is limited by chelate effects, might provide an advantage over the typical more flexible organocatalysts, since the preorganization of the ternary complex must play an important contribution towards lowering the entropic penalty to be paid for the highly organized transition state. We believe that these results demonstrate that the here 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 attractive scaffolds 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. 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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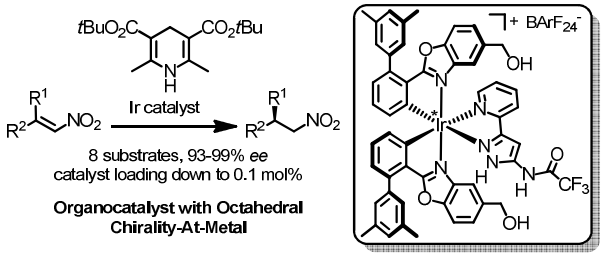
TOC graphic:


tBuO2C
CO2tBu
Ir catalyst
8 substrates, 93-99% ee
catalyst loading down to 0.1 mol%
Organocatalyst with Octahedral
Chirality-At-Metal
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