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Asymmetric Catalysis with Substitutionally Labile yet Stereochemically Stable Chiral-at-Metal Iridium(III) Complex

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Supporting Information

ABSTRACT: A metal-coordination-based high performance asymmetric catalyst utilizing metal centrochirality as the sole element of chirality is reported. The introduced substitutionally labile chiral-at-metal octahedral iridium(III) complex exclusively bears achiral ligands and effectively catalyzes the enantioselective Friedel–Crafts addition of indoles to α,β-unsaturated 2-acyl imidazoles (19 examples) with high yields (75%–99%) and high enantioselectivities (90–98% *ee*) at low catalyst loadings (0.25–2 mol %). Counterintuitively, despite its substitutional lability, which is mechanistically required for coordination to the 2-acyl imidazole substrate, the metal-centered chirality is maintained throughout the catalysis. This novel class of reactive chiral-at-metal complexes will likely be of high value for a large variety of asymmetric transformations.

Metal coordination is arguably one of the most powerful approaches for activating substrates toward chemical transformations. Consequently, chiral metal complexes are employed extensively in industry and academia for the catalytic synthesis of nonracemic chiral compounds.[1] A guiding principle for the design of such metal-coordination-based asymmetric catalysts is the generation of a chiral environment around the metal, which is typically introduced through the association with chiral mono- or multidentate organic ligands. In theory, instead, implementing chirality directly at the reactive metal center—exploiting the metal as a source of centrochirality—would be highly attractive since the close proximity of the metal to the coordinating substrate promises a highly effective transfer of chirality during the asymmetric induction.[2,3] However, a considerable obstacle for the realization of such reactive chiral-at-metal asymmetric catalysts constitutes the retention of the relative and absolute metal-centered configuration during the reaction, since the coordination number at the metal varies during each catalytic cycle and thereby provides ample opportunities for the stereochemistry of the metal to scramble.[1]

We here wish to report the successful sought-after realization of a substitutionally labile (reactive) yet configurationally stable chiral-at-metal high performance asymmetric catalyst.[4] In our design, the metal center serves the dual function of activating a substrate by metal coordination and at the same time comprises the configurationally stable sole element of chirality, thus entirely relying on achiral ligands in the coordination sphere.

Recently, we introduced inert chiral-at-metal iridium(III) complexes as asymmetric catalysts in which the catalysis is mediated through the ligand sphere.[5,6] We hypothesized that the high configurational inertness of iridium(III) complexes might permit retaining metal-centered chirality even in the presence of exchange-labile ligands, and we selected Λ-**1** and Δ-**1** for investigating the scope of asymmetric catalysis with reactive but configurationally stable chiral-at-metal complexes (Figure 1). The C_2-symmetrical complex **1** contains two

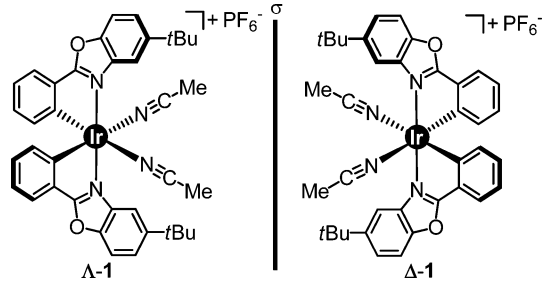

Figure 1. Enantiomers of a substitutionally labile yet configurationally stable chiral-at-metal Ir^{III} complex.

cyclometalating 5-*tert*-butyl-2-phenylbenzoxazoles and two labile acetonitrile ligands. Despite all ligands being achiral, metal-centered chirality leads to a Λ- (left-handed propeller) and Δ-enantiomer (right-handed propeller).

The synthesis of the complexes Λ-**1** and Δ-**1** is straightforward and draws from methodology recently developed in our laboratory.[7−9] Accordingly, the reaction of $IrCl_3 \cdot 3H_2O$ with benzoxazole **2** affords the cyclometalated racemic iridium(III) dimer *rac*-**3** in a diastereoselective fashion (Scheme 1). The subsequent reaction of *rac*-**3** with the chiral auxiliary ligand (*S*)-4-isopropyl-2-(2′-hydroxyphenyl)-2-thiazoline {(*S*)-**4**} provides the two diastereomeric complexes Λ-(*S*)-**5** and Δ-(*S*)-**5** which can be resolved by standard silica gel chromatography, followed by the conversion to virtually enantiopure Λ-**1** and Δ-**1** (each >99% *ee*), respectively, through the stereospecific substitution of the chiral auxiliary ligand (upon protonation by NH_4PF_6) by two acetonitrile ligands.

A crystal structure of Δ-**1** confirms the assigned absolute metal-centered configurations (Figure 2). HPLC traces using a chiral stationary phase are shown in Figure 3 and reveal the high enantiopurity of the synthesized complexes Λ-**1** and Δ-**1**.

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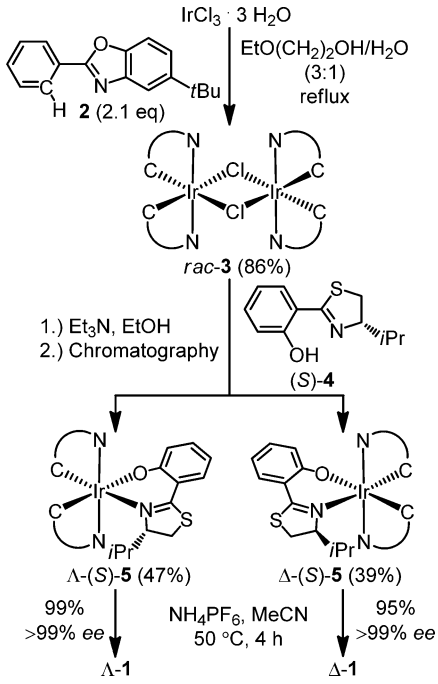
Scheme 1. Synthesis of Complexes Λ-1 and Δ-1



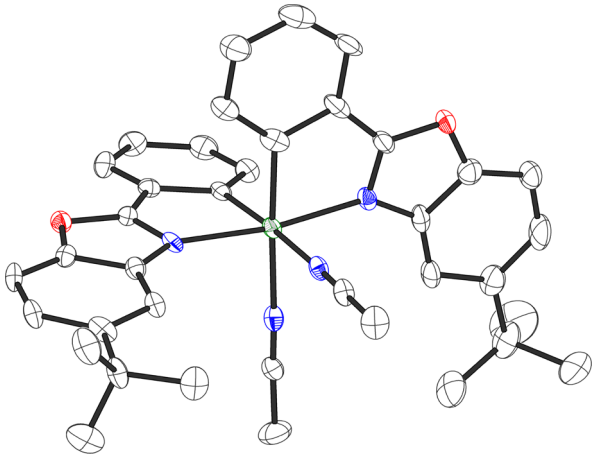


Figure 2. Crystal structure of Δ-1. The hexafluorophosphate counteranion is omitted for clarity. ORTEP drawing with 50% probability thermal ellipsoids.

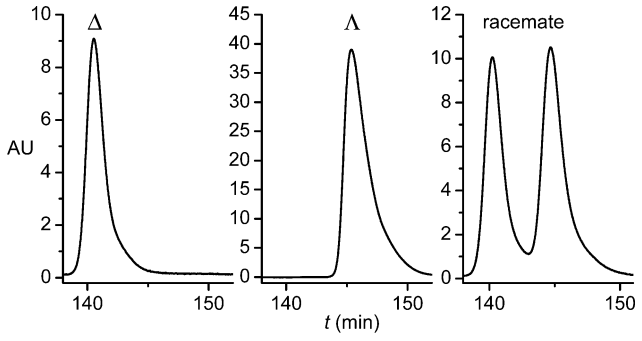
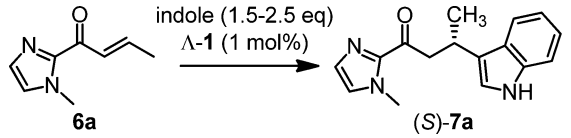


Figure 3. Chiral HPLC traces demonstrating the enantiopurity of synthesized Λ-1 and Δ-1. HPLC conditions: Daicel Chiralcel IB, 250 mm × 4.6 mm, flow rate = 0.5 mL/min, 0.1% aq. TFA with MeCN as eluent (20–43% in 60 min).

Interestingly, these substitutionally labile chiral-at-metal complexes are configurationally stable, as Λ-**1** did not show any significant sign of configurational lability or decomposition upon standing in CH_2Cl_2 on the benchtop for 8 days, as verified by ^{1}H NMR and chiral HPLC analysis (see Supporting Information).

We next investigated the catalytic activity of Λ-**1** and selected the enantioselective Friedel–Crafts alkylation of α,β-unsaturated 2-acyl imidazoles as our model system.[10] Revealingly, the reaction of **6a** with indole (1.5 equiv) in the presence of 1 mol % Λ-**1** afforded the Friedel–Crafts alkylation product (*S*)-**7a** with high enantioselectivity (95% *ee*) albeit with only a slow conversion of just 35% after 20 h at room temperature in MeCN (Table 1, entry 1). A solvent screening revealed that

Table 1. Enantioselective Friedel–Crafts Addition of Indole to α,β-Unsaturated 2-Acyl Imidazole 6a Catalyzed by Λ-1[a]



entry	solvent	conditions	conv (%)[b]	*ee* (%)[c]
1	MeCN	1.5 equiv indole (0.75 M), rt, 20 h	35	95
2	MeOH	1.5 equiv indole (0.75 M), rt, 20 h	70	95
3	CH_2Cl_2	1.5 equiv indole (0.75 M), rt, 20 h	90	94
4	THF	1.5 equiv indole (0.75 M), rt, 20 h	85	96
5	THF	2.5 equiv indole (2.5 M), rt, 20 h	100	96
6	THF	as entry 5 plus air	100	96
7	THF	as entry 5 plus air and 1% H_2O	88	96
8	THF	2.5 equiv indole (2.5 M), 0 °C, 36 h	100	97

[a]Reaction conditions: Imidazole **6a** (0.30 mmol), indole (0.45 or 0.75 mmol), and Λ-**1** (1.0 mol %) in the indicated solvent (0.60 or 0.30 mL) were stirred at the indicated temperature under argon or air. [b]Conversion determined by ^{1}H NMR. [c]Determined by chiral HPLC analysis.

MeOH, CH_2Cl_2, and THF, among others, provide higher catalysis rates (entries 2–4). Optimization of the reaction conditions with THF as the solvent by increasing the concentration of **6a** and the equivalents of indole (2.5 equiv) led to full conversion at room temperature within 20 h and a high *ee* of 96% (entry 5). Interestingly, the reaction is insensitive to air (entry 6) and water (entry 7), and the enantioselectivity can be further improved by reducing the temperature, reaching 97% *ee* at 0 °C (entry 8).

Next, we tested the scope of catalyst Λ-**1**. Table 2 shows that a selection of 13 substituted indoles provide the desired Friedel–Crafts alkylation products (*S*)-**7a–m** with high enantioselectivities (90–98% *ee*) in yields of 75–99% in the presence of 1–2 mol % of Λ-**1** (Table 2). Electron acceptor substituted less reactive indoles require a somewhat increased catalyst loading (2.0 mol %) (entries 4 and 5), while the more reactive 2-methyl indole needs a lower reaction temperature to achieve a high *ee* value (entry 12). The substrate scope with respect to different α,β-unsaturated 2-acyl imidazoles **6b–g** is shown in Table 3 and demonstrates that, upon adjustment of the catalyst loading (1–2 mol % Δ-**1** or Λ-**1**), reaction temperature (0 °C or room temperature), and concentration (1.0 or 2.0 M **6b–g**), very good to excellent enantioselectivities (91–98% *ee*) and yields (78–99%) are achieved for each system (entries 1–6). The α,β-unsaturated 2-acyl imidazole **6g**,

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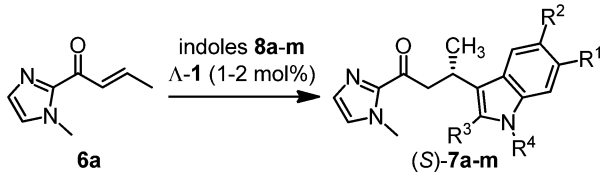
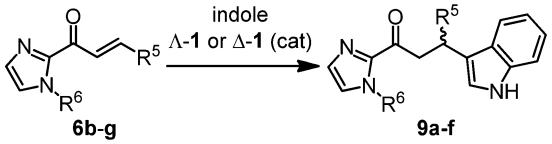
Table 2. Enantioselective Friedel–Crafts Addition of Substituted Indoles to α,β-Unsaturated 2-Acyl Imidazole 6a Catalyzed by Λ-1[a]



	indoles[b]								
entry	R^1	R^2	R^3	R^4	Λ-1 (mol %)	T (°C)	t (h)	yield (%)[c]	*ee* (%)[d]
1	H	H	H	H	1.0	rt	20	97 (**7a**)	96
2	H	Me	H	H	1.0	rt	18	98 (**7b**)	94
3	H	MeO	H	H	1.0	rt	22	99 (**7c**)	94
4	H	Br	H	H	2.0	rt	48	75 (**7d**)	92
5	H	Cl	H	H	2.0	rt	48	77 (**7e**)	94
6	MeO	H	H	H	1.0	rt	18	91 (**7f**)	95
7	H	H	H	Me	1.0	rt	22	99 (**7g**)	96
8	H	H	H	Bn	1.0	rt	22	82 (**7h**)	95
9	H	Me	H	Bn	1.0	rt	18	92 (**7i**)	94
10	H	MeO	H	Bn	1.0	rt	18	91 (**7j**)	94
11	MeO	H	H	Bn	1.0	rt	22	90 (**7k**)	95
12	H	H	Me	Me	2.0	0	36	93 (**7l**)	98
13	H	H	Ph	Me	2.0	rt	40	97 (**7m**)	90

[a]Reaction conditions: Indoles **8a–m** (0.75 mmol), imidazole **6a** (0.30 mmol), and Λ-**1** (1.0 or 2.0 mol %) in THF (0.30 mL) were stirred at the indicated temperature under argon. [b]Indoles **8a–m** consecutively listed from entry 1 to 13. [c]Isolated yields of the indicated products. [d]Determined by chiral HPLC analysis.

Table 3. Enantioselective Friedel–Crafts Addition of Indole to α,β-Unsaturated 2-Acyl Imidazoles 6b–g Catalyzed by Λ-1 or Δ-1[a]



	imidazoles[b]						
entry	R^5	R^6	cat. (mol %)	T (°C)	t (h)	yield (%)[c]	*ee* (%)[d]
1	Et	Me	Δ-**1** (2.0)	0	48	89 (**9a**)	96
2	*n*Bu	Me	Δ-**1** (2.0)	rt	20	97 (**9b**)	91
3[e]	*i*Pr	Me	Δ-**1** (2.0)	rt	48	78 (**9c**)	93
4	Ph	Me	Λ-**1** (1.0)	rt	16	98 (**9d**)	93
5	CO_2Et	Me	Δ-**1** (1.0)	rt	24	97 (**9e**)	98
6	Me	*i*Pr	Δ-**1** (1.0)	rt	24	99 (**9f**)	97
7	Me	*i*Pr	Δ-**1** (0.5)	rt	44	97 (**9f**)	97
8	Me	*i*Pr	Δ-**1** (0.25)	rt	60	91 (**9f**)	97

[a]Reaction conditions: Imidazoles **6b–g** (0.30 mmol), indole (0.75 mmol), and Δ-**1** or Λ-**1** (0.25–2.0 mol %) in THF (0.30 mL) were stirred at the indicated temperature under argon. [b]**6b–g** consecutively listed from entry 1 to 6. [c]Isolated yields of the indicated products. [d]Determined by chiral HPLC analysis. *R*-configuration: entries 1, 2, and 4–8. *S*-configuration: entry 3. [e]Increased concentration of **6c** (2.0 M) in order to speed up the reaction.

bearing an *N*-isopropyl substituent at the imidazole instead of a methyl group, even allows catalyst loading reduction to 0.25 mol % without altering the enantioselectivity (97% *ee*) (entries 6–8). This reflects a respectable turnover number of 364, while not affecting the stereochemical integrity of the metal-centered chirality during all the catalytic cycles.

The C_2-symmetrical iridium complex **1** was designed to serve as a chiral Lewis acid by activating α,β-unsaturated 2-acyl imidazoles through bidentate N,O-coordination. A proposed model for the asymmetric induction in the course of the indole addition that is consistent with the experimental results is shown in Figure 4 and demonstrates that one face of the alkene

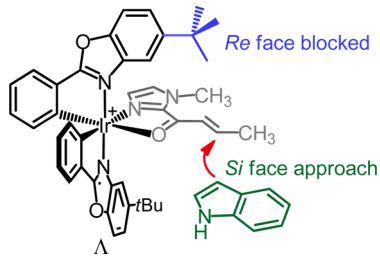


Figure 4. Proposed model for the asymmetric induction in the transition state in which one face of the alkene is blocked by the C_2-symmetrical catalyst.

is sterically shielded effectively by one of the *tert*-butyl groups. It is worth noting that the high lability of the coordinated MeCN ligands of catalyst **1**, which can be confirmed by ^{1}H NMR,[11] is a consequence of the strong *trans*-effect of the Ir–C bonds. Thus, the mechanistic mode of action of catalyst **1** relies on the coordinative lability of the MeCN ligands in combination with the high configurational stability of the remaining octahedral coordination sphere in order to retain the metal-centered chirality at all times.

In conclusion, we here report a novel class of asymmetric transition metal catalysts in which the metal fulfills a dual function by coordinatively activating a substrate and at the same time serving as the sole source of chirality. Whereas typical metal-coordination-based asymmetric catalysts rely on chiral ligands for their asymmetric induction, the here introduced *bis*-

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cyclometalated iridium(III) complex **1** is distinguished by its simplicity, as it just contains two achiral cyclometalating phenylbenzoxazoles and two labile acetonitriles. The high configurational stability of the octahedral iridium chiral center is unexpected considering that labile ligands generally reduce the activation barrier for isomerization. Beyond its conceptual appeal, *bis*-cyclometalated octahedral iridium(III) complex **1** might be of high practical value, as it provides an excellent substrate scope for the highly enantioselective Friedel–Crafts addition of indoles to α,β-unsaturated 2-acyl imidazoles at low catalyst loadings (0.25–2 mol %), while at the same time catalyst **1** displays a high solvent tolerance, does not rely on cryogenic temperatures, and can even be used under open flask conditions.[12] This high performance indicates the value of a direct chirality transfer from the chiral metal to the coordinated substrate. Investigations of reactive chiral-at-metal iridium(III) complexes as catalysts for other asymmetric transformations are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and chiral HPLC traces. 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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