

## Chiral-at-Iron Catalyst: Expanding the Chemical Space for Asymmetric Earth-Abundant Metal Catalysis

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Supporting Information

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ABSTRACT: A new class of chiral iron catalysts is introduced that contains exclusively achiral ligands with the overall chirality being the result of a stereogenic iron center. Specifically, iron(II) is cis-coordinated to two N-(2-pyridyl)-substituted N-heterocyclic carbene (PyNHC) ligands in a bidentate fashion in addition to two monodentate acetonitriles, and the dicationic complex is complemented by two hexafluorophosphate ions. Depending on the helical twist of the PyNHC ligands, the metal center adopts either a  $\Lambda$  or  $\Delta$  absolute configuration. Importantly, the two PyNHC ligands are constitutionally and configurationally inert, while the two acetonitriles are labile and allow asymmetric transition metal catalysis. This is demonstrated with an enantioselective Cannizzaro reaction (96% yield, 88% ee) and an asymmetric Nazarov cyclization (89% yield, >20:1 dr, 83% ee).

hiral transition metal complexes are an important class of asymmetric catalysts and typically synthesized by reacting metal salts or organometallic precursors with carefully tailored chiral ligands (Figure 1a).<sup>1</sup> Recently, an alternative to this modular chiral-ligand-plus-metal design has emerged in which chiral transition metal catalysts exclusively consist of achiral ligands.<sup>2,3</sup> In this approach, the essential overall chirality is the consequence of an asymmetric coordination of the achiral ligands around the central metal, thereby implementing metalcentered chirality (Figure 1b). Proof-of-principle for such chiralat-metal catalysts has been demonstrated recently for the precious metals iridium,<sup>4</sup> rhodium,<sup>5,6</sup> and ruthenium<sup>7,8</sup> by us and others, but the design of reactive chiral-at-metal catalysts based on earth-abundant metals, which have economical and environmental benefits, is elusive.<sup>9</sup> This can be pinpointed to the much higher lability of coordinative bonds of 3d as compared to 4d and 5d transition metals, and it is an unresolved challenge to combine a configurationally inert metal stereocenter with a reactive metal center in a single transition metal catalyst.

The design strategy is especially appealing for its combination of sustainability (base metals)<sup>10</sup> and simplicity (achiral ligands). More importantly, it is expected that without the requirement for chiral structural motifs in the ligand sphere untapped opportunities emerge for the design of earth-abundant metal complexes with new electronic properties and structural architectures that are expected to provide distinct catalytic properties for applications in academia and industry.



Figure 1. Chiral transition metal catalysis. (a) Design from chiral ligands versus achiral ligands. (b) Combining configurational stability of a metal center with some labile ligands. (c) Chiral-at-iron catalyst developed in this study.

Here we report a chiral transition metal catalyst scaffold that is assembled exclusively from achiral mono- and bidentate ligands around the metal iron, the most abundant metal on earth (Figure 1c).<sup>11-13</sup> This work demonstrates the feasibility of designing chiral-at-metal catalysts from earth-abundant metals and provides a blueprint for a whole new class of earth-abundant metal asymmetric catalysts.

The chiral-at-iron catalyst design goes back to related racemic complexes first reported by Hahn.<sup>14</sup> Two N-(2-pyridyl)substituted N-heterocyclic carbene bidentate ligands (PyNHC) provide a helical arrangement with metal-centered  $\Lambda$  (left-handed helix) or  $\Delta$  configuration (right-handed helix). A CF<sub>3</sub> group at the 5-position of the pyridyl group was incorporated to provide steric hindrance for an increased asymmetric induction and to remove electron density for higher configurational and air stability. These two cis-coordinated

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bidentate ligands are complemented by two labile acetonitrile ligands and two hexafluorophosphate counterions. The racemic version of the complex *rac*-**Fe1** was synthesized from elemental iron following a procedure by Chen by converting the imidazolium salt 1 into its silver-carbene complex followed by electrolysis in MeCN using an iron plate as a sacrificial anode to provide *rac*-**Fe1** in a yield of 70% over two steps (Figure 2).<sup>15</sup>



Figure 2. Synthesis of enantiomerically pure chiral-at-iron complexes  $\Lambda$ - and  $\Delta$ -Fe1.

Reaction of the racemic mixture with the chiral auxiliary (*S*)-2 or (*R*)-2 in the presence of Et<sub>3</sub>N provided the complex  $\Lambda$ -(*S*)-Fe2 or  $\Delta$ -(*R*)-Fe2 as single enantiomers in 43% and 42% yield, respectively. Finally, treatment of the individual complexes with NH<sub>4</sub>PF<sub>6</sub> in MeCN at 40 °C afforded the individual enantiomers  $\Lambda$ - and  $\Delta$ -Fe1 in yields of 84% and 83%, respectively.

A crystal structure of  $\Delta$ -**Fe1** is shown in Figure 3 and reveals the relative and absolute metal-centered configuration. Noteworthy are also the interligand  $\pi$ -stacking interactions of the mesityl moieties with the pyridyl groups of the other respective PyNHC ligand. CD spectra shown in Figure 4 furthermore confirm the optical activity and mirror-imaged structures of the complexes  $\Lambda$ - and  $\Delta$ -**Fe1**. The enantiomeric purity of these diamagnetic low-spin complexes was determined to be  $\geq$ 99:1 er by <sup>1</sup>H NMR analysis after coordination to the chiral ligand (*R*)- $\alpha$ -methoxyphenylacetic acid (see Supporting Information).<sup>16</sup>

Importantly, the chiral-at-iron complex Fe1 is constitutionally and configurationally surprisingly robust and can be handled under air without any decomposition. At room temperature in solution overnight,  $\Delta$ -Fe1 does not show any decomposition or racemization as determined by <sup>1</sup>H NMR (see Supporting Information) and CD spectroscopy (Figure 4), respectively.



Figure 3. Single-crystal X-ray structure of  $\Delta$ -Fe1 (CCDC 1892226). ORTEP drawing with 50% probability thermal ellipsoids. Solvent and counterion are omitted for clarity.



Figure 4. Circular dichroism spectra of  $\Lambda$ - and  $\Delta$ -Fe1 (MeCN at 1.0 mM).

This configurational stability, which is clearly distinguished from typical iron(II) complexes<sup>17</sup> with bidentate ligands, can be rationalized with the electronic nature of the PyNHC ligand. A strong  $\sigma$ -donating NHC moiety<sup>18,19</sup> is combined with a  $\sigma$ donating and significantly  $\pi$ -accepting pyridyl ligand, the latter of which is further increased by the electron-withdrawing effect of the CF<sub>3</sub> group.<sup>20</sup> It is established that kinetic and thermodynamic properties of transition metal complexes correlate, among other parameters, with the ligand field stabilization energy, which increases in octahedral complexes with strong  $\sigma$ -donating and  $\pi$ -accepting ligands.<sup>21</sup> At the same time, the kinetic *trans*-effect of the  $\sigma$ -donating NHC ligand assures a high lability of the two acetonitrile ligands.<sup>22</sup> Thus, the cis-coordinated PyNHC ligands with the two MeCN ligands in trans-orientation to the two NHC ligands provide a structural blueprint for combining configurational stability of the metal stereocenter with a high reactivity of the monodentate ligands. The same design principle has already resulted in configurationally very stable chiral-at-ruthenium catalysts,<sup>8</sup> but it was unexpected by us that this can be even applied to the much more labile congener iron.

Next, we investigated the catalytic properties of the new chiral-at-iron complex. Inspired by recent work from Tang on enantioselective intramolecular Cannizzaro reactions of glyoxal monohydrates,  $^{23,24}$  we found that Fe1 can smoothly catalyze the conversion of phenylglyoxal monohydrate (3) to mandelate ester (4) (Table 1). Under optimized reaction conditions, 5 mol

# Table 1. Enantioselective Intramolecular Cannizzaro Reaction Catalyzed by $\Lambda$ - or $\Delta$ -Fe1<sup>*a*</sup>

	Д <sub>он</sub> ,		Δ- or Δ- <b>Fe1</b> (cat		.OR
F	OH (1 3	10 eq) <i>st</i> Cl 4 Å n	andard conditio H <sub>2</sub> Cl <sub>2</sub> (0.05 M), nolecular sieves	ns: r.t. s (MS)	
entry	cat. (mol %)	R	conditions <sup>b</sup>	yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	$\Lambda$ -Fe1 (5.0)	iPr	standard	99 (96) <sup>e</sup>	87.5 (R)
2	$\Delta$ -Fe1 (5.0)	iPr	standard	99	87.0 (S)
3	$\Lambda$ -Fe1 (3.0)	iPr	standard	99	86 (R)
4	$\Lambda$ -Fe1 (3.0)	iPr	no 4 Å MS	0	
5	$\Delta$ -Fe1 (3.0)	iPr	toluene	98	32 (S)
6	$\Delta$ -Fe1 (3.0)	iPr	THF	80	20(S)
7	$\Lambda$ -Fe1 (3.0)	Et <sub>2</sub> CH	standard	50	67 (R)
8	$\Lambda$ -Fe1 (3.0)	<i>t</i> Bu	standard	11	n.d. <sup>f</sup>
9	$\Lambda$ -Fe1 (3.0)	nPr	standard	98	68 (R)
10	$\Lambda$ -Fe1 (3.0)	Et	standard	98	54 (R)
11	$\Lambda$ -Fe1 (3.0)	Me	standard	91	10 (R)

<sup>*a*</sup>Standard conditions: **3** (0.05 mmol), ROH (0.5 mmol), 4 Å MS (25 mg powder), and Fe cat. (0.0015 or 0.0025 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) stirred at rt for 16 h under nitrogen. <sup>*b*</sup>Deviations from standard conditions are shown. <sup>*c*</sup>Determined by <sup>1</sup>H NMR of the crude product using Cl<sub>2</sub>CHCHCl<sub>2</sub> as internal standard. <sup>*d*</sup>Enantiomeric excess determined by HPLC analysis of purified products on a chiral stationary phase. <sup>*c*</sup>Isolated yield in brackets (0.2 mmol scale). <sup>*f*</sup>Not determined.

% A-Fe1, 2-propanol as the alcohol of choice, and 4 Å molecular sieves induced the 1,2-hydride shift at room temperature to provide (*R*)-isopropyl mandelate with 99% NMR yield, 96% isolated yield, and 87.5% ee (entry 1). As expected,  $\Delta$ -Fe1 afforded the mirror-imaged mandelate (*S*)-4 instead (entry 2). Lower catalyst loading resulted in a slightly decreased enantioselectivity (entry 3), whereas molecular sieves are crucial for the conversion (entry 4), and the reaction is very sensitive to the solvent (entries 5 and 6) and the nature of the alcohol (entries 7–11).

Finally, we also investigated an asymmetric Nazarov cyclization and found that **Fe1** can catalyze the cyclization of **5** to **6** (Table 2).<sup>25–27</sup> Under optimized reaction conditions,  $\Lambda$ -**Fe1** (5 mol %) provides (1*R*,2*S*)-**6** in 89% yield, >20:1 dr, and 83% ee (entry 1).<sup>28</sup> Yields and enantiomeric excess are strongly dependent on concentration (entry 2) and the solvent (entries 3–6). Importantly, the ee is not affected by the conversion, which reveals configurational stability of the iron complex throughout the catalysis (see Supporting Information).

In conclusion, we here introduced the first example of an asymmetric iron catalyst that is exclusively composed of achiral ligands with the overall chirality being the result of a stereogenic iron center, implemented and retained by two configurationally surprisingly stable bidentate N-(2-pyridyl)-substituted N-heterocyclic carbene ligands. The chiral-at-iron complex combines sustainability (iron as the metal) and simplicity (easily accessible achiral ligands). Without the requirement for chirality in the ligand sphere, new avenues emerge for the design

Table 2. Asymmetric Nazarov Cyclization Catalyzed by Fe1<sup>a</sup>

		A- <b>Fe1</b> (5 mol%) standard conditions: CH <sub>2</sub> Cl <sub>2</sub> (0.2 M), r.t.		H H H H H CO <sub>2</sub> Me	
entry	5 conditions <sup>b</sup>	c (M)	yield (%) <sup>c</sup>	dr <sup>d</sup> (1R,2	2S)- <b>6</b> ee (%) <sup>e</sup>
1	standard	0.2	89 <sup>f</sup>	>20:1	83
2	standard	0.05	89	>20:1	61
3	HFIP	0.2	81	>20:1	71
4	chloroform	0.2	28	>20:1	34
5	toluene	0.2	5	>20:1	n.d. <sup>g</sup>
6	THF	0.2	0		

<sup>a</sup>Standard conditions: **5** (0.025 mmol) with Fe cat. (0.00125 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.125 mL) stirred at rt for 24 h under nitrogen. <sup>b</sup>Deviations from standard conditions are shown. <sup>c</sup>Isolated yields. <sup>d</sup>Diastereoselective ratio determined by <sup>1</sup>H NMR analysis of the crude product. <sup>c</sup>Enantiomeric excess determined by HPLC analysis of purified products on a chiral stationary phase. <sup>f</sup>Isolated yield from a 0.1 mmol scale reaction. <sup>g</sup>Not determined.

of chiral earth-abundant metal complexes for asymmetric catalysis.

### ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01352.

Experimental details, NMR spectra, and HPLC traces (PDF)

X-ray crystallographic data (CIF)

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#### Notes

The authors declare no competing financial interest.

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