Visible-Light-Activated Enantioselective Perfluoroalkylation with a Chiral Iridium Photoredox Catalyst

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Abstract A visible-light-activated enantioselective radical perfluoroalkylation of 2-acyl imidazoles with perfluoroalkyl iodides (CF3I, C3F7I, C4F9I, C6F13I, C8F17I and C10F21I) and perfluorobenzyl iodide at the α-position of the carbonyl group is reported. Enantioselectivities with up to >99.5% ee are achieved. The process uses a dual-function chiral Lewis acid/photoredox catalyst at loadings of 2–4 mol% and constitutes a re-dox-neutral, electron-catalyzed reaction that proceeds via intermediate perfluoroalkyl radicals.

Key words photoredox catalysis, asymmetric catalysis, visible light, perfluoroalkylation, radical reaction, electron catalysis

Visible-light-driven asymmetric catalysis promises to provide an economical and environmentally sustainable strategy for the synthesis of nonracemic molecules.1 Photocatalysis permits single electron transfer (SET) steps to be induced under very mild reaction conditions, thereby generating intermediate radical ions and radicals with useful reactivities, which expands the mechanistic toolbox for developing novel synthetic transformations.2,3 However, the often very high reactivities and concomitant short lifetimes of these odd-electron intermediates comprise a significant challenge for interfacing them with asymmetric catalysis.4

Recently, our laboratory reported several examples of cooperative photoredox and asymmetric catalysis using a single chiral iridium5–7 or rhodium8 complex, which serves both as a photosensitizer to induce and catalyze redox chemistry and, at the same time, as an asymmetric catalyst. We developed a visible-light-activated enantioselective α-alkylation of 2-acyl imidazoles with electron-deficient benzyl bromides and phenacyl bromides,5 as well as an enantioselective, catalytic trichloromethylation of 2-acyl imidazoles and 2-acylpyridines.6 Here, we further advance the dual-function chiral Lewis acid/photoredox catalyst concept to develop a photoactivated enantioselective perfluoroalkylation9–11 of 2-acyl imidazoles. The photoredox chemistry through intermediate perfluoroalkyl radicals occurs at ambient temperature and requires visible light. High enantioselectivities with up to >99.5% ee are observed.

We initiated our study by investigating the enantioselective perfluoroalkylation of 2-acyl imidazoles by using the previously established dual-function chiral Lewis acid/photoredox catalyst Λ-Ir1 (Table 1).5,7 When 2-acyl imidazole 1a reacted with C6F9I (6 equiv) in the presence of NaHCO3 (1.5 equiv) and 4 mol% Λ-Ir1, the desired α-perfluoroalkylation product 2a' was produced in a disappointing yield of 24% and with unsatisfactory enantioselectivity of 92% ee (entry 1). Increasing the steric congestion of the 2-acyl imidazole by replacing the N-Ph substituent (1a') with N-(2-MePh) (1a) improved the enantioselectivity but the yield remained low (29%; entry 2).

However, we found that replacing Λ-Ir1 with the related catalyst Λ-Ir2 afforded the perfluoroalkylation product 2b with satisfactory yield (78%) and excellent enantioselectivity (99%; Table 1, entry 3). The catalyst loading of Λ-Ir2 could even be reduced to 2 mol% without affecting the performance (entry 4). Control experiments conducted either in the absence of the catalyst or in the dark confirmed that this reaction requires the combined presence of the iridium catalyst and light, otherwise no traces of product were observed (entries 5 and 6). Furthermore, the presence of air completely suppresses the perfluoroalkylation (entry 7), thus supporting the conclusion that this process constitutes a photoredox process that proceeds via intermediate perfluoroalkyl radicals.

The structure of catalyst Λ-Ir2 is shown in Figure 1. This compound bears two cyclometalating 2-phenylbenzothia-zole ligands in addition to two exchange-labile acetonitrile groups; the chirality originates exclusively from metal centroc chirality and thereby creates a C2-symmetrical propeller-
type coordination sphere.\textsuperscript{12,13} Compared with \textit{Ir}_1, \textit{Ir}_2 contains two additional \textit{t}-Bu groups at the phenyl moieties. This modification raises the HOMO and renders \textit{Ir}_2 a better electron donor in both the ground and excited state,\textsuperscript{14} which is apparently beneficial for the perfluoroalkylation reported herein.

![Figure 1](image1.png)

The scope of this reaction with respect to the 2-acyl imidazole substrate is shown in Scheme 1.\textsuperscript{15} Satisfactory yields (59–90\%) and excellent enantioselectivities (96–99\% ee) were achieved for the introduction of a C\textsubscript{6}F\textsubscript{13} substituent into the \(\alpha\)-position of 2-acyl imidazoles, providing the products 3\textsuperscript{a}–\textsuperscript{h} bearing aromatic (3\textsuperscript{a}–\textsuperscript{d}) or aliphatic (3\textsuperscript{e}–\textsuperscript{g}) substituents in the \(\alpha\)-position to the carbonyl group. Even 3\textsuperscript{h}, bearing an aryl ether, was tolerated. We also investigated the scope of the reaction with respect to the perfluoroalkyl groups, synthesizing the perfluoroalkylated products 3\textsuperscript{i}–\textsuperscript{n}. As shown in Scheme 2, C\textsubscript{3}F\textsubscript{7}, C\textsubscript{4}F\textsubscript{9}, C\textsubscript{6}F\textsubscript{13}, and C\textsubscript{10}F\textsubscript{21} substituents can be introduced in a highly enantioselective fashion (3\textsuperscript{i}–\textsuperscript{m}). Furthermore, perfluorobenzylidation (3\textsuperscript{n}) was achieved in 93\% yield, providing virtually only a single enantiomer (>99.5\% ee), demonstrating the high asymmetric induction that can be achieved in this asymmetric photoredox catalysis.

![Figure 1](image2.png)

The proposed mechanism for the perfluoroalkylation involves the intermediate iridium(III) enolate complex that is highlighted in Scheme 3, which is expected to act as the chiral reaction partner for the electron-deficient perfluoroalkyl radicals and, simultaneously, serves as the active photosensitizer (II + h\(\nu\) → II** + e\textsuperscript{-}). Accordingly, coordina-

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**Table 1** Initial Experiments and Optimization of the Visible-Light-Induced Enantioselective Perfluoroalkylation\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Catalyst (mol%)\textsuperscript{b}</th>
<th>Light\textsuperscript{c}</th>
<th>Yield (%)\textsuperscript{d}</th>
<th>ee (%)\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>\textit{Λ}-Ir\textsubscript{1} (4.0)</td>
<td>yes</td>
<td>24</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>\textit{Λ}-Ir\textsubscript{1} (4.0)</td>
<td>yes</td>
<td>29</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>\textit{Λ}-Ir\textsubscript{2} (4.0)</td>
<td>yes</td>
<td>78</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>\textit{Λ}-Ir\textsubscript{2} (2.0)</td>
<td>yes</td>
<td>79</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>\textit{Λ}-Ir\textsubscript{2} (2.0)</td>
<td>no</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>none</td>
<td>yes</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>7\textsuperscript{f}</td>
<td>2-MeC\textsubscript{6}H\textsubscript{4}</td>
<td>\textit{Λ}-Ir\textsubscript{2} (2.0)</td>
<td>yes</td>
<td>0</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1\textit{a} or 1\textit{b} (1 equiv), C\textsubscript{4}F\textsubscript{9}I (6 equiv), NaHCO\textsubscript{3} (1.5 equiv), catalyst (0–4 mol%), MeOH–THF (4:1), r.t., 34–46 h.
\textsuperscript{b} Catalyst loading (mol\%) in parentheses.
\textsuperscript{c} Light source: 21 W compact fluorescent lamp (CFL).
\textsuperscript{d} Isolated yield.
\textsuperscript{e} Determined by chiral HPLC analysis; n.d. = not determined.
\textsuperscript{f} Under air atmosphere.
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The electron that is released upon oxidation of the ketyl intermediate (III → IV + e⁻) either flows into the photoredox cycle by regenerating the oxidized enolate photoredox sensitizer (II⁺ + e⁻ → II) or directly reduces a perfluoroalkyl halide substrate and thereby leads to a chain process. This process can be classified as a redox-neutral, electron-transfer-catalyzed (electron-catalyzed) reaction.17,18

In summary, we have reported a visible-light-activated, highly enantioselective perfluoroalkylation of 2-acyl imidazoles with perfluoroalkyl iodides and perfluorobenzyl iodide. The process uses a dual-function chiral Lewis acid/photoredox catalyst at loadings of 2–4 mol% and constitutes a redox-neutral, electron-catalyzed reaction that proceeds via intermediate perfluoroalkyl radicals. This work demonstrates the generality of the dual-function chiral Lewis acid/photoredox catalyst concept. From the perspective of the catalyst, it is intriguing that the metal center is capable of serving multiple functions at the same time: it constitutes the exclusive center of chirality (only achiral li-

tion of 2-acyl imidazole substrate 1 into Λ-Ir2 under release of the two acetonitrile ligands generates the substrate-coordinated intermediate I, which, upon deprotonation, subsequently converts into the key intermediate, namely enolate complex II. The electron-rich π-system of the enolate double bond enables a rapid reaction with the electron-deficient perfluoroalkyl radicals, which themselves are generated by a SET-reduction of the corresponding perfluoroalkyl halides.16 The highly stereoselective radical addition generates an intermediate iridium-coordinated ketyl III, which is strongly reducing and converts into iridium-coordinated product IV upon oxidation. Release of the product and coordination to a new substrate then leads to a new catalytic cy-

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Scheme 3   Plausible mechanism for the photoactivated asymmetric perfluoroalkylation of 2-acyl imidazoles. The proposed mechanism involves the highlighted intermediate iridium(III) enolate complex, which likely serves as the active photosensitizer and the chiral reaction partner for the electron-deficient radicals.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561284.

References and Notes


(3) For reactions involving single-electron transfer, see: Zhang, N.; Samanta, S. R.; Rosen, B. M.; Percec, V. Chem. Rev. 2014, 114, 5848.


(9) For perfluoroalkylations through photoredox chemistry, see:


(15) General photolysis procedure: A dried 10 mL Schlenk tube was charged with catalyst Λ-Ir2 or Δ-Ir2 (2 or 4 mol%), NaHCO3 (25.2 mg, 0.3 mmol, 1.1 equiv), and the corresponding 2-acyl imidazole (0.2 mmol, 1.0 equiv). The tube was purged with nitrogen and MeOH–THF (4:1, 0.5 mL) was added by using a syringe, followed by the perfluoroalkyl iodide (6–10 equiv). The reaction mixture was degassed in three freeze-pump-thaw cycles, then the vial was sealed and positioned approximately 5 cm from a 21 W compact fluorescent lamp (CFL). The reaction was stirred at room temperature for the indicated time (monitored by TLC) under a nitrogen atmosphere.

