GDCh Highlights Angewandte Chemie International Edition

Photocatalysis

International Edition: DOI: 10.1002/anie.201511443
German Edition: DOI: 10.1002/ange.201511443

A Chiral Metal Photocatalyst Architecture for Highly Enantioselective Photoreactions

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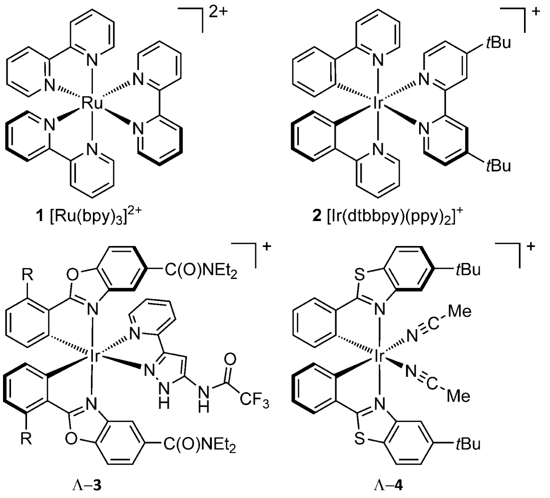
asymmetric catalysis · chirality · photocatalysis · radical reactions

Control over the stereochemistry of organic reactions has been a central theme of contemporary synthetic chemistry for many decades. Almost every class of organic transformations has now been shown to be amenable to high levels of stereocontrol using an assortment of structurally diverse chiral catalyst architectures. Unfortunately, photochemical reactions are an exception to this general trend: Despite significant efforts, the design of catalysts that promote highly enantioselective photochemical transformations has proven to be a challenging goal.[1] Many possible rationales for the greater difficulty of controlling stereochemistry in photochemical reactions have been offered. The high-energy intermediates involved in photochemical reactions often have very short lifetimes and can be difficult to influence with exogenous catalysts. These intermediates are also structurally quite dissimilar from the substrates involved in more conventional, thermally initiated reactions and thus may necessitate the use of different catalyst geometries for optimal stereocontrol. Whatever the reason, high enantioselectivities have only recently become reasonably common in catalytic photochemical synthesis.

Many of the recent successes in enantioselective photochemical reactions have arisen in the context of a renewed interest in the synthetic application of octahedral Ru^{II} and Ir^{III} complexes as catalysts for photoinduced electron transfer (see Figure 1, catalysts **1** and **2**).[2] These "photoredox" catalysts absorb light to produce redox-active excited states, which in turn can initiate a wide range of reactions by facile one-electron oxidation or reduction processes. Remarkably, this class of octahedral transition-metal catalysts has proven to be well-suited for dual-catalytic applications in which the photoredox catalyst is combined with a second, stereocontrolling catalyst. Chiral organocatalysts and Lewis and Brønsted acids have been employed as co-catalysts to control the reactivity of various photocatalytically generated reactive intermediates.[3] Notably, the photoredox catalysts themselves, though chiral, have almost exclusively been used in racemic form. There have been only a few instances in which the stereochemistry of the metal center itself has been investigated for its ability to influence the enantioselectivity of photoredox reactions, with generally low levels of stereoinduction.[4]



1 [Ru(bpy)$_3$]$^{2+}$

2 [Ir(dtbbpy)(ppy)$_2$]$^+$

Λ-**3**

Λ-**4**

Figure 1. Octahedral Ru^{II} and Ir^{III} complexes.

For the past several years, Meggers and co-workers have been interested in the use of chiral-at-metal iridium complexes as enantioselective catalysts for organic transformations. Their early work explored these chiral architectures as scaffolds that enable the positioning of catalytic hydrogen-bonding, amine nucleophile, or Brønsted acid functional groups in a conformationally rigid, stereochemically well-defined space (for example, catalyst Λ-**3**; Figure 1).[5] In these studies, the inert metal center simply provided a rigid structural framework and was not directly involved in the catalysis of the reaction. Subsequently, Meggers and co-workers showed that a similar chiral-at-metal iridium complex bearing hemilabile acetonitrile ligands could be used as a chiral Lewis acid catalyst for conjugate addition reactions (complex Λ-**4**).[6] Notably, this complex maintained its metal-centered stereochemistry despite the rapid ligand exchange necessary for good catalytic activity.

In a very recent set of papers, the Meggers group has demonstrated that chiral-at-metal iridium complexes can also be competent visible-light photoredox catalysts. The Ir complexes used in this work play a dual role as both a Lewis acid and a photocatalyst (Scheme 1). For example, in the

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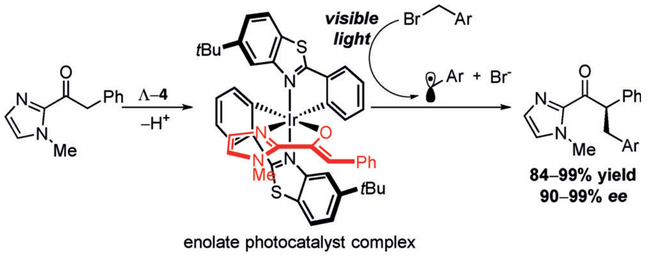
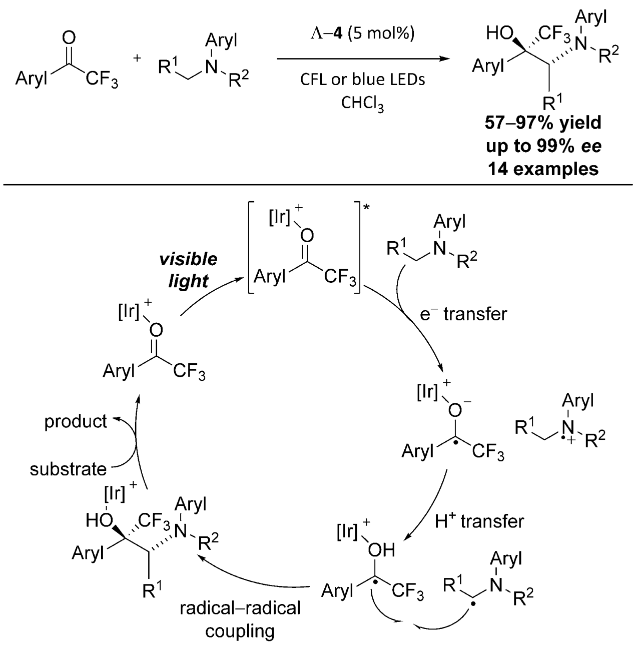


Scheme 1. Initial report of chiral-at-metal iridium photocatalysts by Meggers and co-workers.

initial report in this series,[7] Ir complex Λ-**4** first acts as a Lewis acid catalyst to promote the enolization of an acyl imidazole substrate. The resulting enolate/Lewis acid complex then serves as the active photocatalytic species; upon photoexcitation, the triplet Ir complex promotes one-electron reduction of a benzylic halide to afford an electrophilic radical intermediate. This radical intercepts another equivalent of the enolate complex, resulting in the formation of a new α-C–C bond with exceptionally high levels of stereocontrol, consistent with the enantioselectivities observed in non-photochemical reactions involving **4**. Subsequent reports have utilized the same general concept for the enantioselective functionalization of ketones with radicals produced by other photoredox processes.[8]

The enantioselective capture of photochemically generated electrophilic radicals has become a subject of increasing interest over the past several years. Photoredox methods reported by MacMillan[9] and co-workers are conceptually the most related to Meggers' work; however, in MacMillan's strategy, a separate chiral amine co-catalyst is used to control the stereochemistry of the radical attack. This approach has the benefit of enabling optimization of the stereochemistry-controlling organocatalyst without impacting the photophysical properties of the photocatalyst, and vice versa. The use of a single chiral photocatalyst, as in Meggers' approach, is somewhat more challenging because changes to the structure of the catalyst impact both enantioselectivity and photophysical properties at the same time. The fact that a number of highly enantioselective photoreactions could nevertheless be achieved with Meggers' chiral-at-metal Ir complexes is evidence of their exceptional capacity for stereoinduction.

In a very recent report, the Meggers laboratory has now demonstrated that a chiral iridium complex can be an enantioselective photocatalyst for the synthesis of chiral 1,2-amino alcohols by a radical–radical cross-coupling reaction (Scheme 2).[10] The proposed mechanism for this transformation is fundamentally distinct from the electrophilic radical chemistry invoked for Meggers' prior work and involves photoinduced electron transfer from a tertiary aryl amine to a catalyst-bound ketone. Whereas a variety of aromatic amines could be used in this reaction, only heteroaryl trifluoromethyl ketones that are quite electron-deficient proved to be suitable substrates for this transformation. The authors rationalized this observation by proposing that the resulting stabilized ketyl radical is a so-called "persistent radical" that possesses relatively little propensity towards homodimerization. A characteristic of the reactivity of this class of radicals is their ability to participate in radical–radical heterocouplings. In the case of the mechanism proposed by Meggers, the photogenerated amine radical interacts with the persistent ketyl radical within the chiral environment of the Ir complex, which provides impressively high enantioselectivity in this context as well.



Scheme 2. New radical–radical coupling reported by Meggers and co-workers (top). Proposed mechanism (bottom).

This most recent work is contemporaneous with a dual-catalyst approach towards photocatalytic radical–radical coupling developed by Ooi and co-workers, who utilized a separate photoredox catalyst in combination with a chiral Brønsted acid co-catalyst.[11] Both approaches have attractive qualities; Meggers' one-catalyst system exhibits greater operational simplicity, whereas Ooi's two-catalyst method highlights the compatibility of photoredox catalysis with yet another family of chiral co-catalysts, in this case, the chiral hydrogen-bonding scaffold developed by his laboratory. In the context of enantioselective photoredox chemistry, it seems best to consider these two strategies as important conceptual complements to one another.

However, the remarkable feature emerging from Meggers' studies of this chiral iridium catalyst architecture is its success in two mechanistically distinct photoreactions, in dramatic contrast to the relatively limited scope of previous attempts to use chiral photocatalysts in enantioselective photochemical synthesis. When one also considers the high enantioselectivities obtained by using this catalyst architecture in non-photochemical applications, it becomes increasingly clear that these chiral-at-metal octahedral Ir complexes exhibit a surprising generality as asymmetric catalysts across many diverse applications. One might wonder whether this catalyst architecture might represent a new privileged structure for asymmetric catalysis. The availability of such structures is highly valued in the search for new enantioselective reactions, and the discovery of fundamentally new privileged catalyst structures is a rare event.[12] The possibility that these Ir complexes might be such a privileged structure that provides a broadly applicable solution to the long-standing challenge of stereoinduction in photochemical reactions is an exciting one.

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2304–2306
Angew. Chem. **2016**, *128*, 2348–2350

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Received: December 9, 2015