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Photoredox Catalysis

A Rhodium Catalyst Superior to Iridium Congeners for Enantioselective Radical Amination Activated by Visible Light

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Abstract: A bis-cyclometalated rhodium(III) complex catalyzes a visible-light-activated enantioselective α-amination of 2-acyl imidazoles with up to 99% yield and 98% *ee*. The rhodium catalyst is ascribed a dual function as a chiral Lewis acid and, simultaneously, as a light-activated smart initiator of a radical-chain process through intermediate aminyl radicals. Notably, related iridium-based photoredox catalysts reported before were unsuccessful in this enantioselective radical C–N bond formation. The surprising preference for rhodium over iridium is attributed to much faster ligand-exchange kinetics of the rhodium complexes involved in the catalytic cycle, which is crucial to keep pace with the highly reactive and thus short-lived nitrogen-centered radical intermediate.

Reactions involving single-electron-transfer (SET) steps have sparked much attention over the last several years.[1] Two reasons account for this renaissance: 1) the transfer of single electrons to or from closed shell molecules leads to intermediate radical ions, whose strongly modulated reactivity can be exploited for the design of reactions with novel mechanisms;[2] 2) visible-light photosensitization offers a sustainable, convenient, and very mild method to initiate the transfer of single electrons.[3] However, the cooperation of such photoredox chemistry with asymmetric catalysis poses significant challenges due to the high reactivity and limited lifetimes of radical ion and radical intermediates, indicated by the still limited number of catalytic asymmetric photoredox systems.[4]

MacMillan recently reported a photoinduced enantioselective α-amination of aldehydes using (ODN)-*N*-functionalized carbamates (ODN = 2,4-dinitrophenylsulfonyloxy) catalyzed by chiral secondary amines. This process was proposed to proceed through the intermediate formation of electron-deficient aminyl radicals and their stereocontrolled reactions with chiral enamine intermediates, constituting a rare example of an enantioselective catalysis exploiting the reactivity of nitrogen-centered radicals.[5] Inspired by this work, we envisioned that chiral transition-metal enolates might serve as related intermediates to react with aminyl radicals in an asymmetric fashion as a means to devise a visible light-activated catalytic, enantioselective C–N bond formation.[6] Here we report our surprising finding that a bis-cyclometalated rhodium(III) complex[7] serves as a highly effective visible-light-activated catalyst for the enantioselective radical amination of 2-acyl imidazoles (Figure 1). Notably, related bis-cyclometalated iridium(III) complexes, which were previously demonstrated to serve as dual photoredox/chiral Lewis acid catalysts for enantioselective C–C bond formation reactions,[8–10] are not suitable for the here described enantioselective C–N bond formation chemistry.

We recently developed the asymmetric photoredox alkylation of 2-acyl pyridines and 2-acyl imidazoles using iridium complexes that serve a dual function as catalytically active chiral Lewis acids and as visible-light-triggered photoredox catalysts.[8–10] Consequently, our study was initiated by investigating the reaction of 2-acyl imidazole **1a** with the ODN-carba-

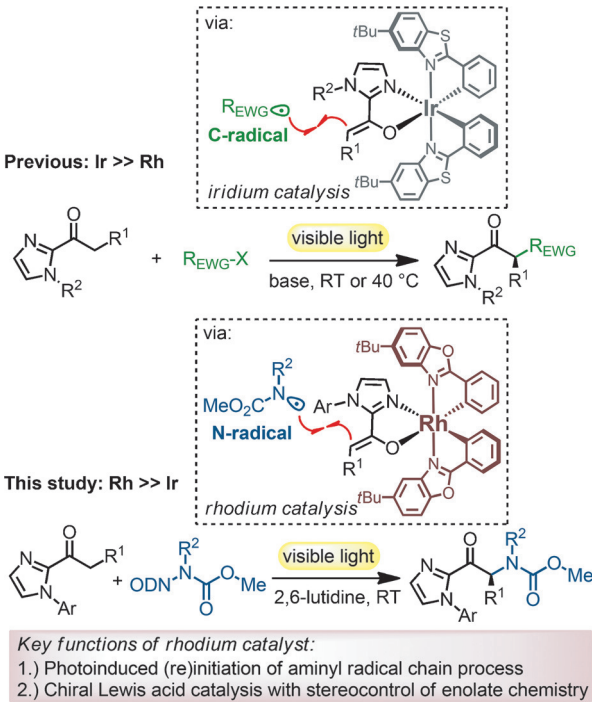

Figure 1. Previous and presented work regarding catalytic enantioselective photoredox chemistry with single transition-metal complexes (ODN = 2,4-dinitrophenylsulfonyloxy).

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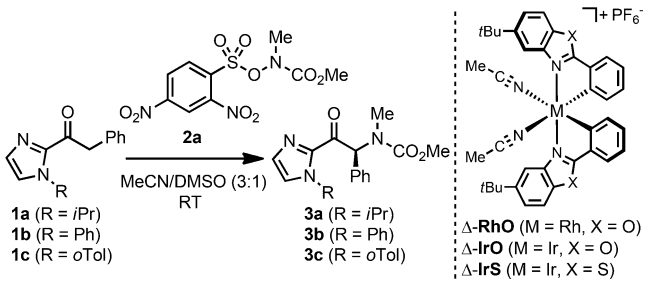
mate **2a** in the presence of the previously disclosed photoredox catalysts Δ-**IrS**[8,10] (2.0 mol%) or Δ-**IrO**[9] (2.0 mol%) under irradiation with blue LEDs, but failed to provide useful amounts of C–N bond formation product despite extensive efforts (Table 1, entries 1 and 2). However, to our surprise and delight, when we tried instead the rhodium complex Δ-**RhO**[7] (2.0 mol%), the α-aminated 2-acyl imidazole **3a** was obtained with 44% yield and 80% *ee* (entry 3). Replacing the isopropyl substituent of the imidazole moiety with phenyl (**1b**) improved the yield to 93% with 89% *ee* (entry 4). Using an *ortho*-tolyl substituent (**1c**) also provided an excellent 96% yield and 97% *ee* (entry 5). Intriguingly, a short photolysis time with blue LEDs of just 2 h is sufficient to achieve full conversion. The reaction can also be activated with a regular compact fluorescent light bulb (CFL), although the reaction time doubles to 4 h (entry 6). Lower catalyst loadings afford the C–N formation product in somewhat reduced yield but still with high enantioselectivity (entries 7 and 8). Importantly, control experiments in the absence of either light (entry 9) or rhodium catalyst (entry 10) fail to provide any product, thereby demonstrating that this catalytic, enantioselective C–N bond formation crucially depends on both the chiral rhodium complex and visible light. As further control experiments, simple Lewis acids such as $Sc(OTf)_3$ or $Mg(OTf)_2$ are inferior in catalyzing this reaction, even at tenfold higher catalyst loadings (entries 11 and 12, see also Supporting Information).

Table 1. Initial experiments of visible-light-induced enantioselective C–N bond formation.[a]



entry	catalyst[b]	*h*ν source[c]	R	*t* [h]	yield [%][d]	*ee* [%][e]
1	Δ-**IrO** (2.0)	blue LEDs	*i*Pr	12	0	n.d.
2	Δ-**IrS** (2.0)	blue LEDs	*i*Pr	12	0	n.d.
3	Δ-**RhO** (2.0)	blueLEDs	*i*Pr	12	44	80
4	Δ-**RhO** (2.0)	blue LEDs	Ph	2	93	89
5[f]	Δ-**RhO** (2.0)	blue LEDs	*o*Tol	2	96	97
6	Δ-**RhO** (2.0)	CFL	*o*Tol	4	94	97
7	Δ-**RhO** (1.0)	blue LEDs	*o*Tol	6	71	97
8	Δ-**RhO** (0.5)	blue LEDs	*o*Tol	10	65	95
9	Δ-**RhO** (2.0)	none	*o*Tol	16	0	n.d.
10	none	blue LEDs	*o*Tol	16	0	n.d.
11	$Sc(OTf)_3$ (20)	blue LEDs	*o*Tol	2	21[g]	n.d.
12	$Mg(OTf)_2$ (20)	blue LEDs	*o*Tol	2	2[g]	n.d.

[a] Conditions: **1a–c** (0.40 mmol), **2a** (0.20 mmol) and 2,6-lutidine (0.34 mmol) with or without catalyst in MeCN/DMSO (3:1, 1.0 mL) under nitrogen. [b] Catalyst loading in mol% given in parentheses. [c] 24 W blue LEDs or 20 W CFL (white light). [d] Isolated yields. [e] Determined using chiral HPLC analysis; n.d. = not determined. [f] When executed under air for 6 h, a reduced yield of 38% with 97% *ee* was obtained. [g] Yields estimated by ^{1}H NMR.

Table 2 displays a brief substrate scope, revealing that substituents are well tolerated on the aromatic moiety, which is in the α-position to the carbonyl group (Table 2, entries 1–6), although a *para*-methoxy group reduces the yield and requires higher catalyst loadings (entry 7). Furthermore, a naphthyl moiety affords the C–N formation product in 81% yield with 96% *ee* (entry 8), and more bulky ODN-carbamates **2b-d** (entries 9–11) provide excellent results, particularly with an isobutyl group at the nitrogen (**2d**) affording the α-amination product in 99% yield with 98% *ee*. However, it has to be noted that this reaction only works with aromatic substituents in the α-position to the carbonyl group (entry 12), presumably to lower the pK_a value of the methylene group. Finally, we would like to mention that the reaction is scalable. On a one-gram scale in a flow system, we obtained for the reaction of **1c**+**2a**→**3c** a yield of 90% with 97% *ee* with a reaction time of 3 h.

Table 2. Substrate scope.[a]

entry	R^1	R^2	*t* [h]	yield [%][b]	*ee* [%][c]
1	4-FPh (**1d**)	Me (**2a**)	1.5	99 (**3d**)	97
2	4-ClPh (**1e**)	Me	2	98 (**3e**)	98
3	3-ClPh (**1f**)	Me	2	89 (**3f**)	92
4	2-ClPh (**1g**)	Me	2	99 (**3g**)	97
5	4-BrPh (**1h**)	Me	2	97 (**3h**)	97
6	4-MePh (**1i**)	Me	6	81 (**3i**)	97
7[d]	4-MeOPh (**1j**)	Me	5	52 (**3j**)	97
8	2-naphthyl (**1k**)	Me	2	81 (**3k**)	96
9	phenyl (**1c**)	*n*Bu (**2b**)	2	82 (**3l**)	97
10	phenyl	$Ph(CH_2)_3$ (**2c**)	2	88 (**3m**)	96
11	phenyl	*i*Bu (**2d**)	2	99 (**3n**)	98
12	Me (**1l**)	Me	38	0 (**3o**)	n.d.

[a] Reaction conditions: **1c–l** (0.40 mmol), **2a–d** (0.20 mmol) and 2,6-lutidine (0.34 mmol) with Δ-**RhO** (2.0 mol%) in MeCN/DMSO (3:1, 1.0 mL) were irradiated with blue LEDs (24 W) under nitrogen. [b] Isolated yields. [c] Determined by chiral HPLC analysis; n.d. = not determined. [d] 5.0 mol% catalyst loading instead.

We propose the following mechanism, as shown in Figure 2. The acyl imidazole substrate coordinates to the rhodium catalyst in a bidentate fashion (intermediate **I**) followed by a deprotonation of the α-methylene group, which affords a neutral rhodium enolate complex (intermediate **II**). We believe that this enolate **II** has a crucial dual function. Firstly, it serves as an initiator and reinitiator, dubbed a "smart initiator" by Studer and Curren,[11] upon photoactivation (**II**+hν→**II***) by transferring a single electron (**II***→$\mathbf{II}^+$+e^-) to the ODN-carbamate, which then fragments into a sulfonate anion and an aminyl radical.[12] Secondly, enolate **II** contains a very electron-rich double bond that reacts with the electrophilic nitrogen-centered radical in a stereocontrolled fashion.[13,14] This provides a rhodium-coordinated ketyl (intermediate **III**), which is highly reducing and either donates an electron to the photoredox

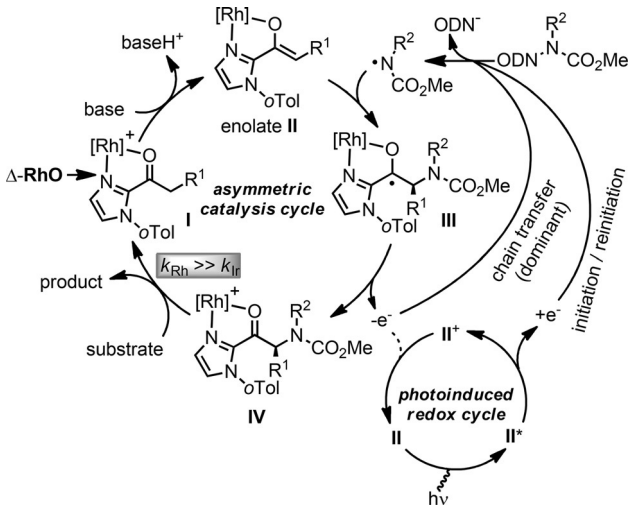
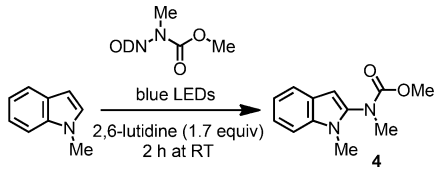


Figure 2. Proposed mechanism for the visible light-activated enantioselective rhodium catalysis.

Table 3. Verification of the formation of intermediate nitrogen-centered radicals by trapping experiments.[a]



entry	catalyst	yield [%][b]
1	**RhO** (2 mol%)/**1 b** (20 mol%)	61
2	**RhO** (2 mol%)	6
3	no transition metal catalyst	4
4	**IrO** (2 mol%)/**1 b** (20 mol%)	77
5	**IrS** (2 mol%)/**1 b** (20 mol%)	78

[a] Reaction conditions: *N*-methylindole (0.20 mmol), **2 a** (0. 10 mmol), 2,6-lutidine (0.17 mmol), together with the indicated amounts of **1 b** and catalyst in MeCN/DMSO (3:1, 0.5 mL) irradiated with blue LEDs (24 W) for 2 h under nitrogen. [b] Yields are determined with ^{1}H NMR using an internal standard.

cycle to regenerate the oxidized rhodium enolate (**II**$^+$+e$^-$→**II**) or directly transfers a single electron to the ODN-carbamate, thereby propagating a chain process.

A number of experiments strongly support this mechanism. We obtained a crystal structure of the proposed enolate intermediate **II** and confirmed its catalytic competence (see Supporting Information). A reduced yield in the presence of oxygen (Table 1, entry 5) as well as a suppression of product formation (below 10%) in the presence of TEMPO (5 equivalents) support a radical mechanism (see Supporting Information). Furthermore, a calculated quantum yield of 14 for this photochemical reaction lends support to a chain mechanism in which the electron transfer from the ketyl intermediate **III** to the ODN-carbamate dominates. Considering nonproductive quenching and energy decay processes of the photoexcited rhodium-enolate complex **II**, chain cycles of 100 or even higher can be assumed for this reaction.[15]

Trapping reactions with *N*-methylindole as shown in Table 3 provide further important insights into the mechanism: 1) The observed amination of the 2-position (leading to **4**) is indicative of a radical reaction through intermediate nitrogen-centered radicals; 2) **RhO** is an effective catalyst only in the presence of catalytic amounts of 2-acyl imidazole (Table 3, entries 1 and 2), which is consistent with our proposal that the intermediate rhodium enolate complex **II** is responsible for the light-activated reductive formation of the nitrogen radical;[16] 3) in the complete absence of any transition-metal catalyst, only small amounts of product are formed, thus revealing that MacMillan's proposed mechanism[5] of a direct activation of the ODN-carbamate is not operative in our system; 4) for **IrO** and **IrS** in the presence of some 2-acyl imidazole, the indole amination product was obtained in high yields upon visible-light activation (Table 3, entries 4 and 5). This means that the incompetence of the established dual-function chiral Lewis acid/photoredox catalysts **IrO**[9] and **IrS**[8,10] to catalyze the enantioselective C–N bond formation of **1**+**2**→**3** is not related to the photoredox-induced formation of the nitrogen-centered radical intermediate.

The superiority of **RhO** over its iridium congeners in this reaction can rather be pinpointed to kinetic effects, namely the requirement of a high turnover frequency of the catalytic cycle. Amidyl radicals are known to be highly reactive electrophilic π-type radicals[17] that add to electron-rich alkenes much faster than carbon-centered radicals.[18,19] Such electrophilic nitrogen-centered radicals are also highly prone to reduction.[19] A concomitant short lifetime and fast reaction of the nitrogen-centered radical intermediate with the rhodium enolate **II** requires a fast turnover frequency of the catalytic cycle to regenerate new **II** rapidly enough to be a reaction partner for the aminyl radical. Indeed, comparison of initial rates for an exchange of the acetonitrile ligands against substrate in **RhO** versus **IrO** demonstrates an increased rate constant for ligand exchange of the rhodium complex by >1650-fold (Figure 3). On the other hand, the inferior photophysical properties of bis-cyclometalated rhodium over iridium complexes,[20] resulting in a less efficient rhodium photoredox-sensitizer, is not relevant for this reaction owing to a highly efficient chain propagation, as demonstrated by the observed high quantum yield. Thus, the rhodium enolate intermediate **II** serves as a smart initiator,[11] which is needed to initiate and, from time to time, reinitiate the chain reaction after chain termination.

In conclusion, we have introduced a very efficient photoactivated enantioselective radical amination of 2-acyl imidazoles catalyzed by a chiral-at-metal rhodium complex, which serves a dual function, namely as a chiral Lewis acid to catalyze asymmetric enolate chemistry and, furthermore, as a light-activated smart initiator of a radical chain process. Intriguingly, under related conditions, previously developed iridium complexes fail to work in this context. This is attributed to much faster ligand exchange kinetics in the rhodium system, which are required to match the high reactivity and short lifetime of the intermediate nitrogen-centered radicals. The inferior photoredox properties of the rhodium system do not play a role here due

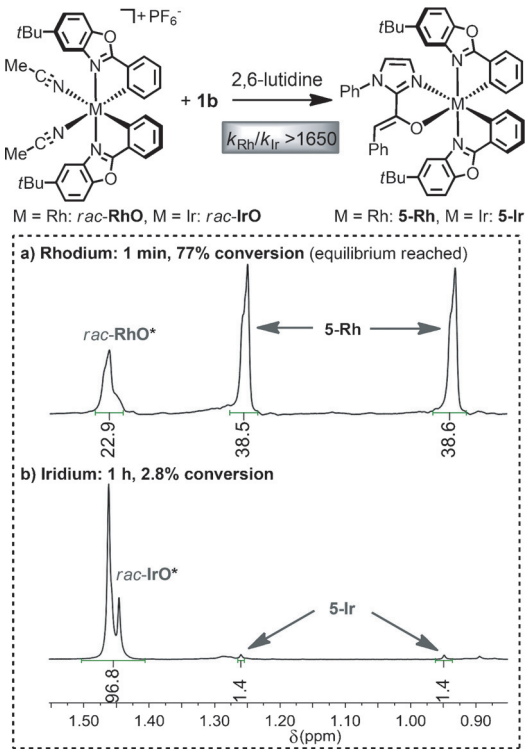


Figure 3. Ligand exchange kinetics. *Some exchange of MeCN for DMSO.

to an efficient chain mechanism. Thus, this work demonstrates the importance of finely tuned kinetics for radical formation, propagation, and regeneration of key catalytic intermediates in photoredox catalysis.

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Keywords: asymmetric · catalysis · photoredox · visible light

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