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Asymmetric Catalysis with Organic Azides and Diazo Compounds Initiated by Photoinduced Electron Transfer

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Abstract: Electron-acceptor-substituted aryl azides and α-diazo carboxylic esters are used as substrates for visible-light-activated asymmetric α-amination and α-alkylation, respectively, of 2-acyl imidazoles catalyzed by a chiral-at-metal rhodium-based Lewis acid in combination with a photoredox sensitizer. This novel proton- and redox-neutral method provides yields of up to 99% and excellent enantioselectivities of up to >99% ee with broad functional group compatibility. Mechanistic investigations suggest that an intermediate rhodium enolate complex acts as a reductive quencher to initiate a radical process with the aryl azides and α-diazo carboxylic esters serving as precursors for nitrogen and carbon-centered radicals, respectively. This is the first report on using aryl azides and α-diazo carboxylic esters as substrates for asymmetric catalysis under photoredox conditions. These reagents have the advantage that molecular nitrogen is the leaving group and sole by-product in this reaction.

INTRODUCTION

There is a constant demand in organic synthesis for the enantioselective construction of C-N/C-C bonds. In particular, a variety of elegant synthetic methodologies have been developed to build carbonyl compounds bearing an α-amino/alkyl group, greatly promoted by their wide distribution in natural products and biological active molecules.[1] Among these strategies, visible-light-induced electron transfer provides a mild and powerful tool to generate highly reactive radicals and radical ions for C-N/C-C bond formation.[2-4] However, controlling the stereochemistry with such reactive intermediates,[5-7] along with the need to prevent postreaction racemization of products, makes visible-light activated asymmetric α-amination/alkylation of ketones a considerable challenge.

As a result, limited examples of visible-light-induced catalytic asymmetric α-alkylation of ketones are reported, which employ organic bromides/iodides[8] or α-silylalkylamines[9] as alkylation reagents with stoichiometric amount of base or oxidant, respectively (Figure 1a). Recently, two studies used *N*-2,4-dinitrophenylsulfonyloxy functionalized carbamates as nitrogen radical source to achieve an enantioselective α-amidation of aldehydes and ketones with the addition of equivalent amounts of base and the release of a sulfonate anion as by-product (Figure 1a).[10] Despite great progress, the development of new reagents for the effective asymmetric construction of C-N/C-C bond with higher atom economy and milder conditions is still highly desirable.

Organic azides[11] and diazo compounds[12] are unique and highly versatile building blocks and widely used as environmentally benign amination/alkylation reagents featuring the advantage of N_2 as leaving group and sole by-product under redox-neutral conditions. Despite some examples of these reagents used in the context of photoredox reactions,[13,14] the manipulation of these high-energy synthons under visible-light conditions in an enantioselective manner remains elusive. Two main reasons might be responsible for this: First, azides and diazo compounds typically generate respective nitrene and carbene intermediates under photochemical activation resulting in potential side reactions and narrow functional group compatibility,[15] and second, the highly negative

reduction potential of organic azides and diazo compounds makes them difficult to be reduced under mild conditions.[16]

Herein, we introduce aryl azides and α-diazo carboxylic esters as radical precursors for asymmetric catalysis under photoredox conditions for the first time (Figure 1b). A chiral-at-metal rhodium Lewis acid catalyst in combination with a photoredox sensitizer enables chemoselective and enanotioselective α-amination and α-alkylation of ketones with good functional group tolerance. This method is redox- and proton-neutral and molecular nitrogen is the only by-product in these reactions.

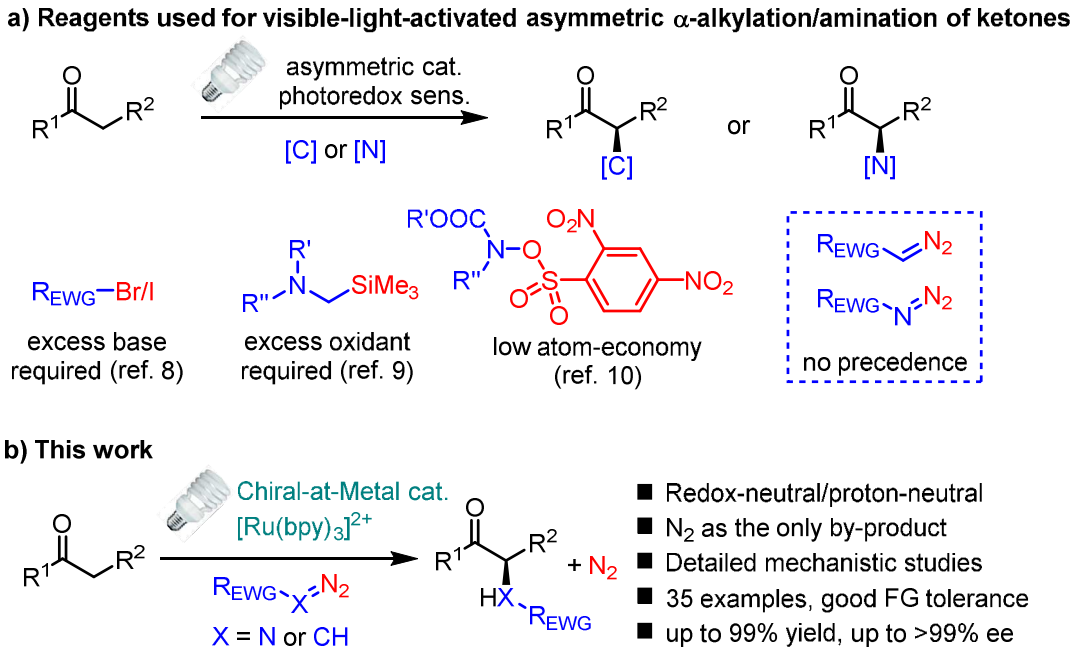


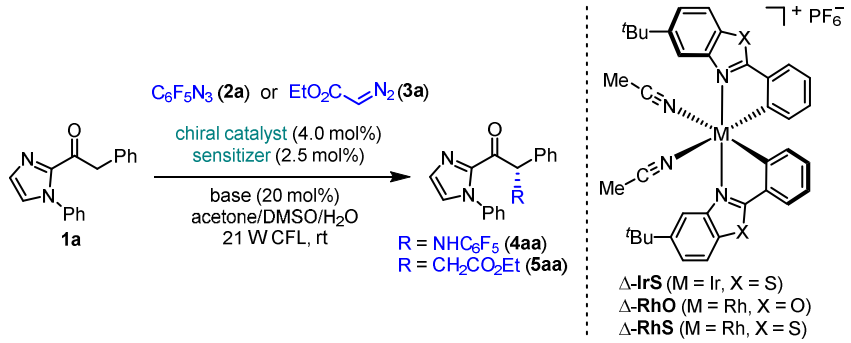
Figure 1. Established strategies and this work regarding visible-light-activated asymmetric α-alkylation/amination of ketones.

RESULTS AND DISCUSSION

Initial Experiments. In line with our research using chiral-at-metal complexes as photoredox/Lewis acid catalysts,[6c,i] we started this investigation with the reaction of 2-acyl imidazole **1a** and pentafluorophenyl azide **2a** in the presence of catalytic amounts of diisopropylethylamine (DIPEA) (Table 1). Although our well-developed dual functional catalyst Δ-**IrS** did not show any reactivity (entries 1-2), we speculated that the recently introduced combination of a chiral-at-metal rhodium-based Lewis acid catalyst with a separate photoredox sensitizer could provide access to desired amination product **4aa**.[6i] Indeed, the chiral Lewis acid catalyst Δ-**RhO** (4.0 mol%) together with $[Ru(bpy)_3](PF_6)_2$ (2.5 mol%) in the presence of visible light afforded the amination product **4aa** in a low yield of just 24% but with encouraging 86% ee (entry 3). Revealingly, the related catalyst Δ-**RhS**,[17] in which the benzoxazole ligands are replaced by benzothiazoles, provided **4aa** with 70% yield and 97.7% ee (entry 4). Other Lewis acids, such as $Sc(OTf)_3$, $FeCl_3$, and $Cu(OAc)_2$, could not catalyzed the racemic reaction, highlighting the unique reactivity of chiral-at-metal **RhS** in this transformation (Table S7). Other photoredox sensitizers, such as $[Ir(ppy)_2(dtbbpy)](PF_6)$ and *fac*-$Ir(ppy)_3$, showed lower efficiency (entries 4-6). A further optimization of the reaction conditions (entries 7-11 and Supporting Information) resulted in the identification of Na_2HPO_4 as the preferred base, providing 82% yield and 98.4% ee for the reaction **1a** + **2a** → **4aa** (entry 10). While a base is required (entry 11), it is noteworthy that K_3PO_4 led to product decomposition (entry 9 and Table S4), indicating that **4aa** is very sensitive to strong basic conditions. Control experiments confirm that the chiral Lewis acid, the photoredox sensitizer, and visible light are all indispensable in this process (entries 12-14).

Encouraged by these positive amination results, we became interested in investigating the current catalytic system with related diazo compounds. Indeed, the alkylation product **5aa** was obtained in excellent yield (93%-94%) with 92% ee when ethyl diazo acetate **3a** was used instead of azide **2a** under similar reaction conditions, thus demonstrating the versatility of this newly developed catalytic system in enolate chemistry (entries 15-16).

Table 1. Optimization of the Reaction Conditions[a]



entry	reagent	chiral cat.	sensitizer	base	hν[b]	yield (%)[c]	ee (%)[d]
1[e]	**2a**	Δ-**IrS**	-	DIPEA	yes	0 (**4aa**)	n.a.
2[e]	**2a**	Δ-**IrS**	$[Ru(bpy)_3](PF_6)_2$	DIPEA	yes	0 (**4aa**)	n.a.
3[e]	**2a**	Δ-**RhO**	$[Ru(bpy)_3](PF_6)_2$	DIPEA	yes	24 (**4aa**)	86
4[e]	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	DIPEA	yes	70 (**4aa**)	97.7
5[e]	**2a**	Δ-**RhS**	$[Ir(ppy)_2(dtbbpy)](PF_6)$	DIPEA	yes	62 (**4aa**)	97.8
6[e]	**2a**	Δ-**RhS**	*fac*-$Ir(ppy)_3$	DIPEA	yes	37 (**4aa**)	89
7	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	DIPEA	yes	77 (**4aa**)	98.1
8	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	2,6-lutidine	yes	73 (**4aa**)	98.0
9	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	K_3PO_4	yes	0 (**4aa**)	n.a.
10	**2a**	**Δ-RhS**	**$[Ru(bpy)_3](PF_6)_2$**	**Na_2HPO_4**	**yes**	**82 (4aa)**	**98.4**
11	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	-	yes	0 (**4aa**)	n.a.
12	**2a**	-	$[Ru(bpy)_3](PF_6)_2$	Na_2HPO_4	yes	0 (**4aa**)	n.a.
13	**2a**	Δ-**RhS**	-	Na_2HPO_4	yes	0 (**4aa**)	n.a.
14	**2a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	Na_2HPO_4	-	0 (**4aa**)	n.a.
15	**3a**	Δ-**RhS**	$[Ru(bpy)_3](PF_6)_2$	Na_2HPO_4	yes	93 (**5aa**)	92
16[f]	**3a**	**Δ-RhS**	**$[Ru(bpy)_3](PF_6)_2$**	**Na_2HPO_4**	**yes**	**94 (5aa)**	**92**

[a]Reaction conditions: **1a** (0.10 mmol), **2a** or **3a** (0.30 mmol), chiral catalyst (4.0 mol%), sensitizer (2.5 mol%), base (20 mol%), and H_2O (20 equiv) in acetone/DMSO (9:1, 0.2 M) were stirred at room temperature for 8-16 h under visible light. [b]Light source: 21 W CFL. [c]Isolated yields. [d]Determined by HPLC on a chiral stationary phase. [e]Acetone/DMSO (4:1, 0.2 M) was employed. [f]1.5 mol% of $[Ru(bpy)_3](PF_6)_2$ was employed. DIPEA = diisopropylethylamine; n.a. = not applicable; bpy = 2,2'-bipyridine; ppy = 2-phenylpyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine.

Mechanistic Investigations. Based on previous studies[6i,8h,10b] and the requirement for a base we expect that the reaction proceeds through a rhodium enolate intermediate. To support this assumption, the **Rh-enolate** was synthesized independently, characterized by X-ray diffraction, and tested for its competence as catalyst in the amination and alkylation reactions (Figure 2a). Indeed, comparable yields were observed with **Rh-enolate** as the catalyst in the absence of any base, thus being consistent with the rhodium enolate serving as a key intermediate in these transformations.

Next, four sets of experiments support that the reaction proceeds through a radical pathway rather than a nitrene/carbene process. First, both amination and alkylation were completely inhibited by air together with the generation of the oxygenation product **6**, which implies that α-carbonyl carbon radicals derived from imidazole substrate might be involved (Figure 2b, eq 1).[18] Second, when silyl enolate **7** was added to the reaction mixture of **1b** and **2a**, the C-C and C-N bond formation products **8** (42% yield) and **9** (22% yield) were isolated, respectively (Figure 2b, eq 2), indicating the intermediate formation of α-carbonyl carbon radicals and aminyl radicals. Third, when TEMPO was added to the reaction mixture of **1b** and **3a**, the TEMPO adducts **10** (84% yield) and **11** (6% yield) were isolated (Figure 2b, eq 3), being indicative for two types of intermediate α-carbonyl carbon radicals. Fourth, the isolation of the radical addition product **12** instead of the cyclopropanation product **13** in the reaction with ethyl diazo acetate **3a** renders a mechanism through carbene intermediates unlikely (Figure 2c). The intermediate formation of the cyclopropanation compound was ruled out by the independent synthesis of **13** and re-subjection to the standard photoredox conditions under which no reaction occurred (see Supporting Information for more details).

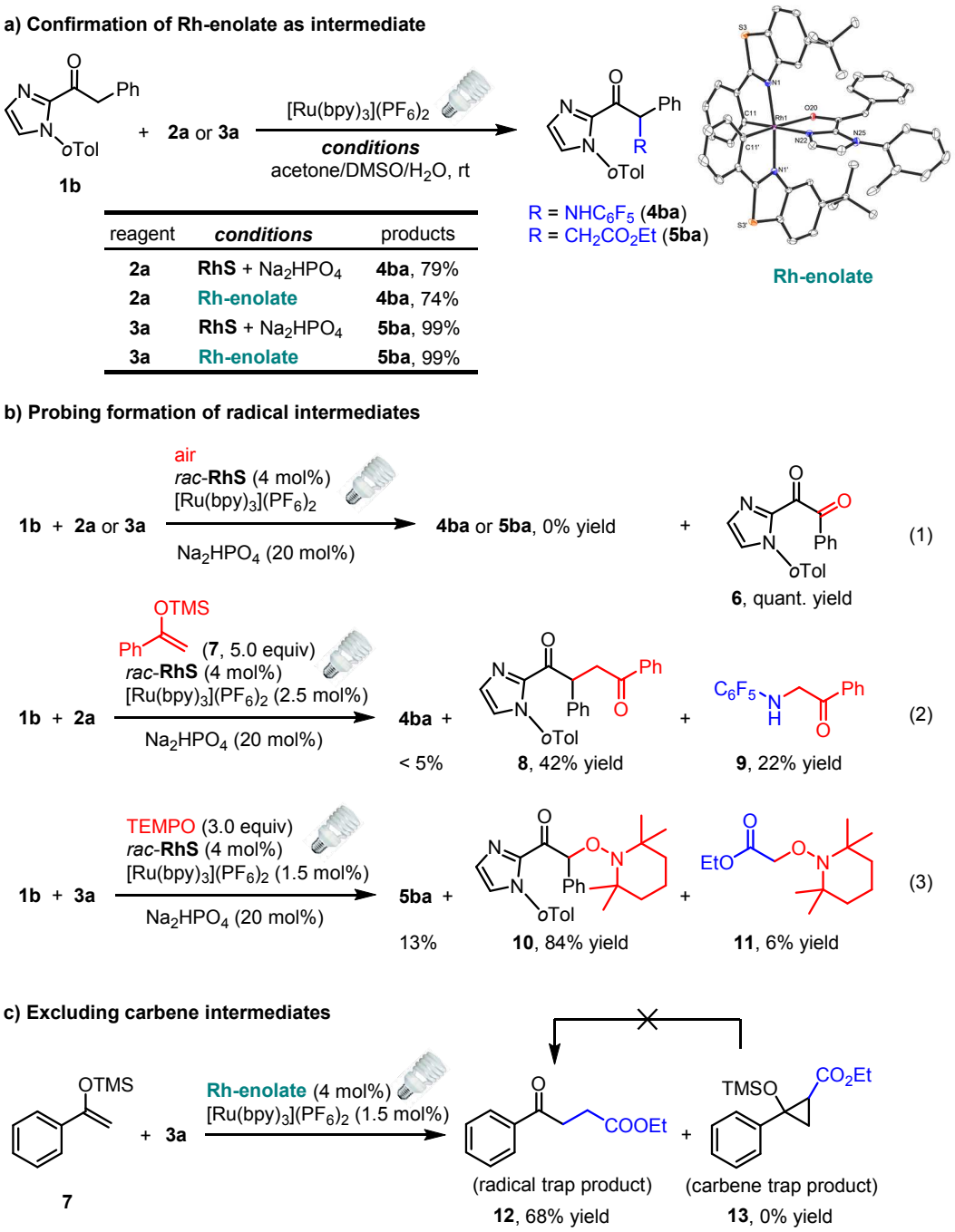


Figure 2. Mechanistic experiments.

In order to further confirm a radical pathway in this photoredox reaction, the alkylation reaction was monitored by electron paramagnetic resonance (EPR) spectroscopy. With the addition of DMPO as free radical spin-trapping agent, signals with 6 lines (g=2.006; α_N = 15.9 G, α_H^{β} = 22.5 G) were observed and identified as EPR signals of adduct **14**, which is in good agreement with the literature (Figure 3).[19] All these results support the formation of an ethyl acetate α-carbon radical through single electron reduction of the diazo compound **3a**, suggesting that the mechanism is distinct from recent work by Gryko and coworkers in which a direct reaction between an intermediate radical and a diazo compound was proposed.[14]

Furthermore, we were seeking to verify the initial electron transfer (SET) step of the photoredox process and therefore performed a series of Stern-Volmer quenching experiments (Figure 4 and SI). These studies showed that only the intermediate **Rh-enolate** but no other component, including the catalyst **RhS** and the silyl enolate **7**, is capable of quenching the excited state of the photosensitizer $[Ru(bpy)_3]^{2+}$ (PS) and this most likely through a reductive quenching cycle ($E_{1/2}^{PS*/PS-}$ = +0.77 V vs SCE in MeCN).[2a] This is in agreement with cyclic voltammetry which reveals that **Rh-enolate** (E_p^{ox} = 0.078 V vs Fc/Fc^+ in MeCN) has a significantly lower oxidation peak potential than **RhS** (E_p^{ox} = 1.25 V vs Fc/Fc^+ in MeCN) (Figure 5). On the other hand, the reduction peak potential of **2a** or **3a** is too negative[16] so that **2a** or **3a** cannot quench the excited state of $[Ru(bpy)_3]^{2+}$ ($E_{1/2}^{PS+/PS*}$ = -0.81 V vs SCE in MeCN)[2a] by an oxidative quenching cycle. All these results strongly suggest that SET between the rhodium enolate and excited $[Ru(bpy)_3]^{2+}$ is a key step of the photoredox cycle. A SET reduction of **2a** or **3a** by $[Ru(bpy)_3]^{+}$ ($E_{1/2}^{PS/PS-}$ = -1.33 V vs SCE; < -1.7 V vs Fc/Fc^+)[20] appears also feasible.[16]

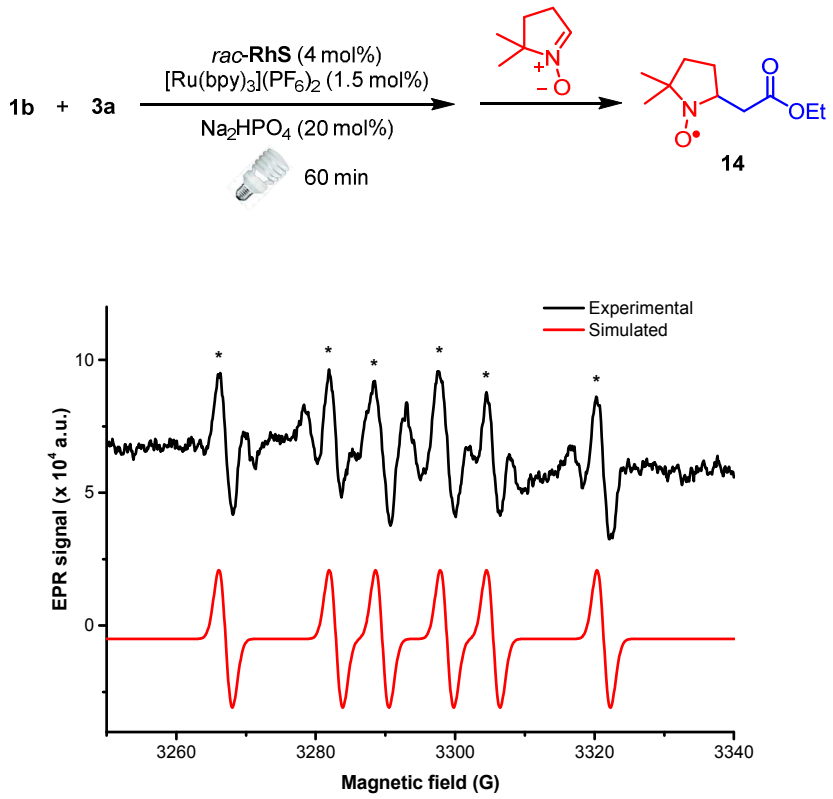


Figure 3. EPR spectra (X band, 9.7 GHz, r.t.) of spin adduct **14** generated under conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), *rac*-**RhS** (4.0 mol%), $[Ru(bpy)_3](PF_6)_2$ (1.5 mol%), Na_2HPO_4 (20 mol%) and H_2O (20 equiv) in acetone/DMSO (9:1, 0.2 M) were stirred at room temperature under visible light; after 60 min stirring, DMPO solution was added and then analyzed by EPR.

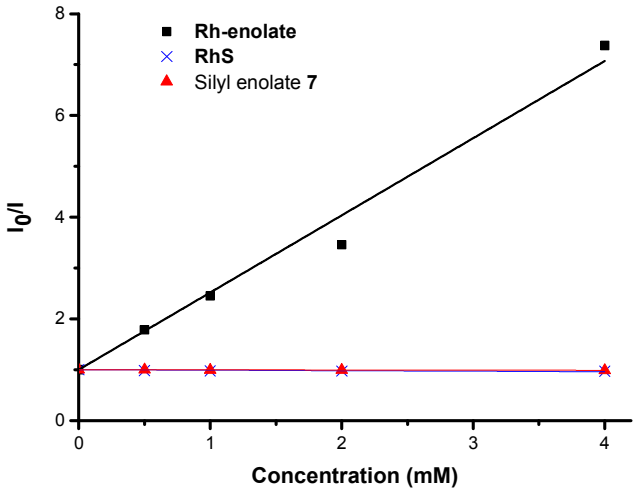


Figure 4. Stern-Volmer quenching experiments with photoexcited $[Ru(bpy)_3]^{2+}$ (0.5 mM, λ_{ex} = 530 nm, λ_{em} = 610 nm). I_0 and I are respective luminescence intensities in the absence and presence of the indicated concentrations of the corresponding quencher. Silyl enolate **7** = trimethyl((1-phenylvinyl)oxy)silane.

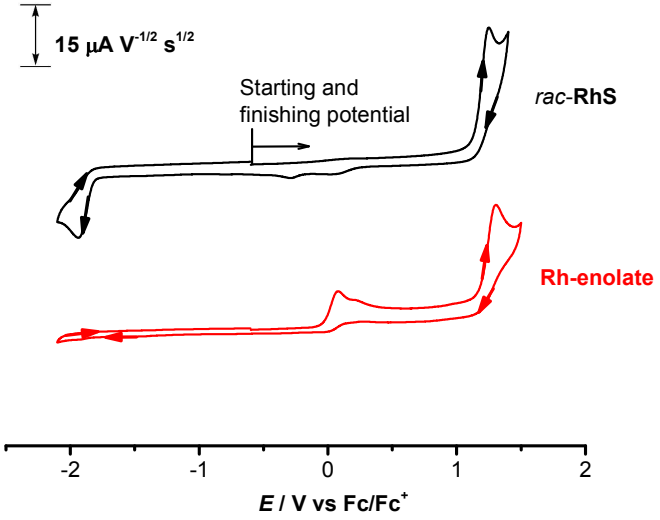


Figure 5. Cyclic voltammograms of **RhS** and **Rh-enolate** recorded in CH_3CN containing 0.1 M *n*-Bu_4NPF_6 at 22 ± 2 °C. Scan rate = 0.1 V s^{-1}.

Based on above results, a mechanism consisting of the cooperation between a photoredox and an asymmetric catalysis cycle is given in Figure 6. Substrate coordination to **RhS** (intermediate **A**) and base-induced deprotonation generates the electron-rich rhodium enolate **B**, which initially serves as the single electron donor for photoexcited $[Ru(bpy)_3]^{2+}$ (**B** → $\mathbf{B_{ox}}$ + e^-), thereby generating strongly reducing $[Ru(bpy)_3]^{+}$ which in turn transfers a single electron to the organic azide or diazo substrate. Sequential N_2 extrusion and protonation produces nitrogen- or carbon-centered radicals, respectively.[13a] The subsequent stereoselective addition of these electron-deficient radicals to the electron-rich double bond of the rhodium enolate **B** constitutes the chirality generating step and provides the Rh-coordinated ketyl radical **C**. The ketyl **C** is a strong reducing agent and either directly reduces the azide/diazo reagent to afford chain propagation[21] or quenches photoexcited $[Ru(bpy)_3]^{2+}$ to produce the reduced photoredox sensitizer $[Ru(bpy)_3]^{+}$.[22] The oxidation of ketyl **C** leads to Rh-coordinated product (intermediate **D**), which after product release and re-coordination of new substrate engages in a new catalytic cycle.

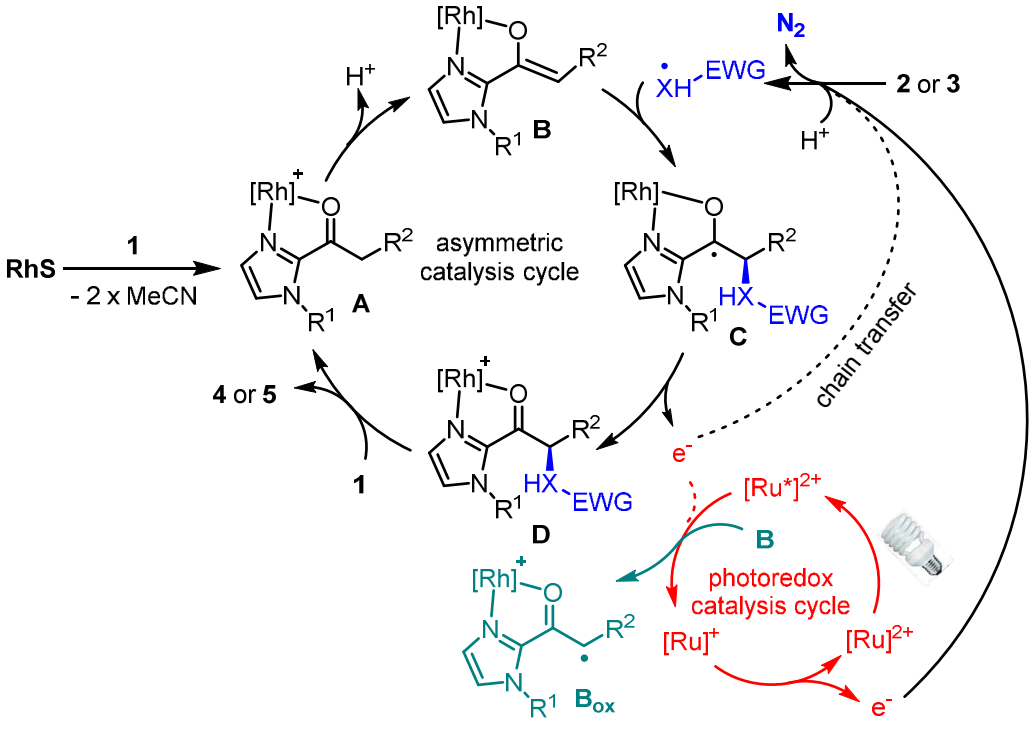
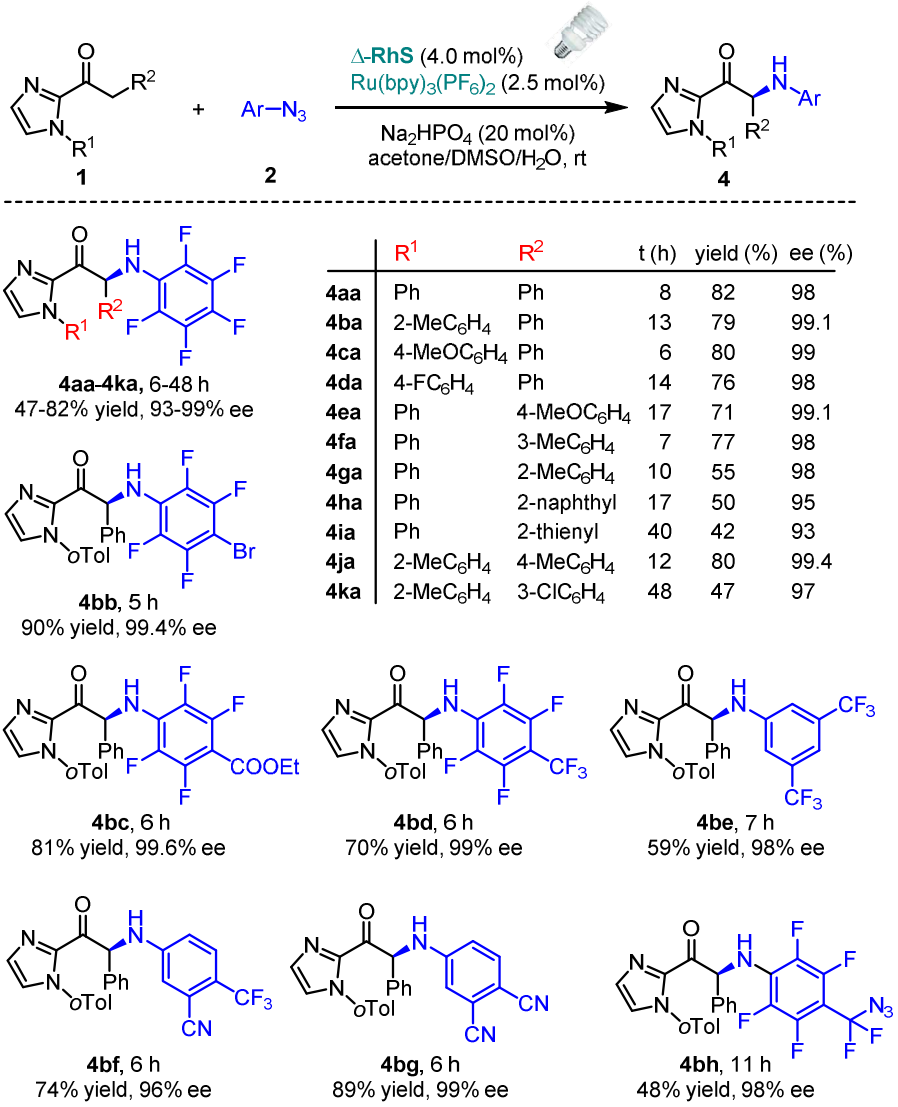


Figure 6. Proposed mechanism.

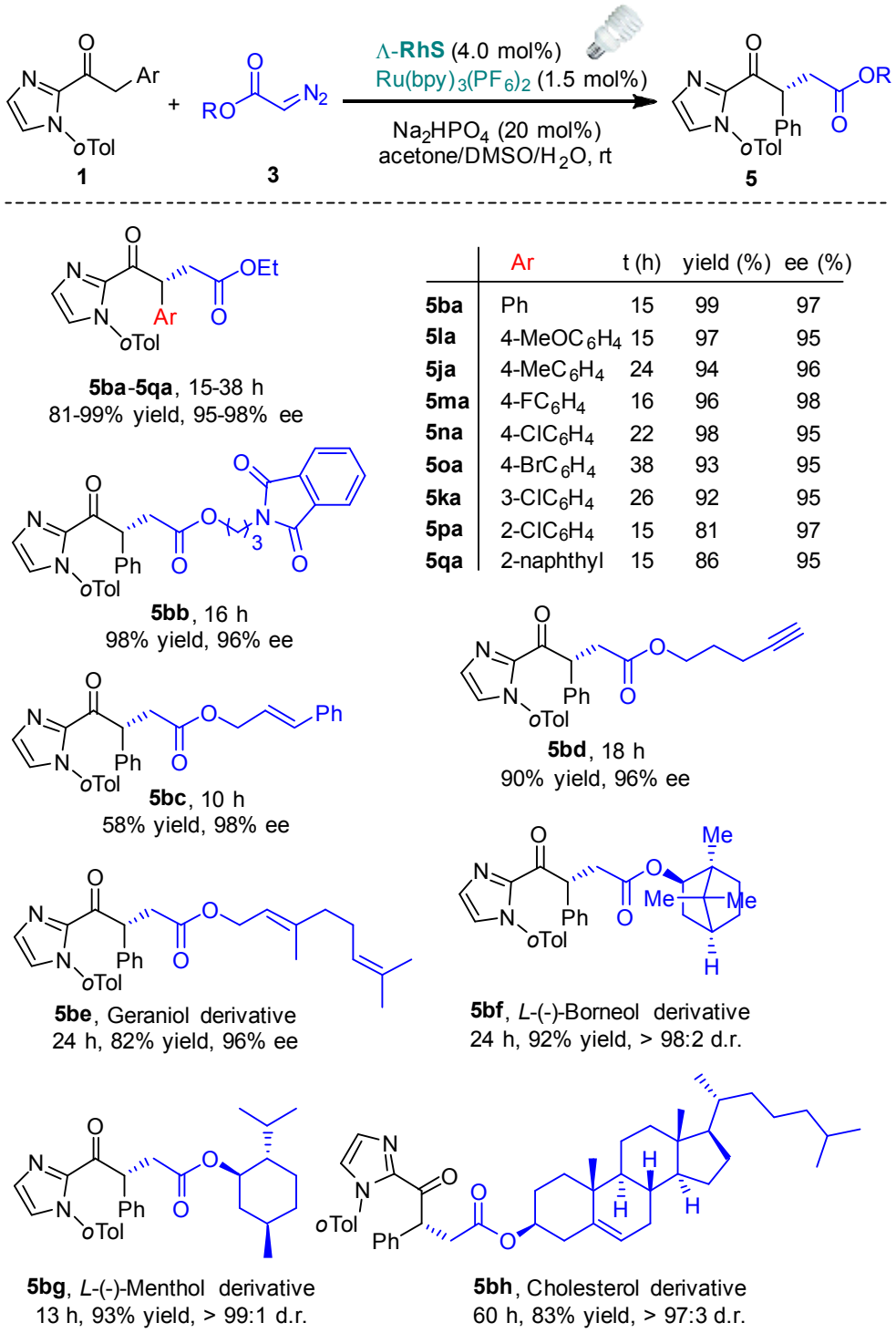
Substrate Scope. Having addressed the mechanism, we next explored the substrate scope of amination with aryl azides under optimal conditions (entry 10, Table 1). As shown in Figure 7, good yields and excellent enantioselectivities were obtained in the amination of 2-acyl imidazoles with different substituents at the N-atom of imidazole (**4aa**-**4da**) or different electron-rich aromatic groups at the stereogenic carbon (**4ea**-**4ga**, **4ja**). Other functional groups, such as naphthyl (**4ha**), thienyl (**4ia**), and chloride (**4ka**), are well tolerated giving moderate yields and satisfying enantioselectivities. On the other hand, a wide range of electron-deficient aromatic azides performed well both in yields and enantioselectivities (**4bb**-**4bg**). Remarkably, bromo (**4bb**) and cyano groups (**4bf**-**4bg**), which are vulnerable to reducing conditions, are compatible under the present mild protocol, providing the potential for further transformations. Intriguingly, chemoselective amination with an aryl azido group over an aliphatic azido group was observed (**4bh**). Notably, 8 examples of these amination products were formed with an enantioselectivity of 99% ee or even higher without any postreaction racemization.

Finally, the substrate scope with respect to enantioselective alkylation with α-diazo carboxylic esters under photoredox conditions was evaluated (Figure 8). Accordingly, the alkylation of a variety of 2-acyl imidazoles worked well, providing asymmetric 1,4-diketones in good to excellent yields (81-99%) with excellent enantioselectivities (95-98% ee), regardless of the electronic nature or position of substituents (**5ba**-**5qa**). As expected from the perspective of the mechanism, CC double and triple bonds were found to be well tolerated (**5bc**-**5be**, **5bh**). Notably, we were pleased to find that the present asymmetric alkylation was compatible with various natural alcohol derivatives (**5be**-**5bh**), highlighting the broad substrate scope and the potential utility of this protocol in further late-stage functionalization. In addition, the removal of the imidazole moiety of **5ba** worked smoothly, giving 1,4-diester **15** in 81% yield with little loss in enantiomeric excess (95% ee, eq 4).[23]



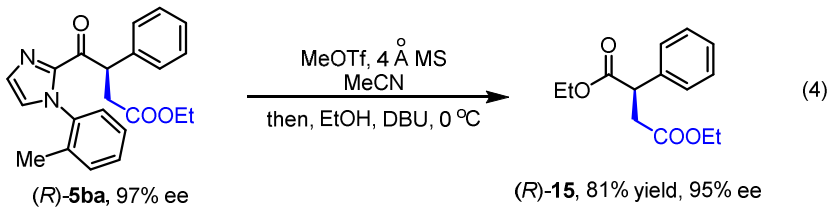
	R^1	R^2	t (h)	yield (%)	ee (%)
4aa	Ph	Ph	8	82	98
4ba	2-MeC_6H_4	Ph	13	79	99.1
4ca	4-$MeOC_6H_4$	Ph	6	80	99
4da	4-FC_6H_4	Ph	14	76	98
4ea	Ph	4-$MeOC_6H_4$	17	71	99.1
4fa	Ph	3-MeC_6H_4	7	77	98
4ga	Ph	2-MeC_6H_4	10	55	98
4ha	Ph	2-naphthyl	17	50	95
4ia	Ph	2-thienyl	40	42	93
4ja	2-MeC_6H_4	4-MeC_6H_4	12	80	99.4
4ka	2-MeC_6H_4	3-ClC_6H_4	48	47	97

Figure 7. Substrate scope for enantioselective amination with aryl azides. See SI for detailed conditions.



	Ar	t (h)	yield (%)	ee (%)
5ba	Ph	15	99	97
5la	4-MeOC$_6$H$_4$	15	97	95
5ja	4-MeC$_6$H$_4$	24	94	96
5ma	4-FC$_6$H$_4$	16	96	98
5na	4-ClC$_6$H$_4$	22	98	95
5oa	4-BrC$_6$H$_4$	38	93	95
5ka	3-ClC$_6$H$_4$	26	92	95
5pa	2-ClC$_6$H$_4$	15	81	97
5qa	2-naphthyl	15	86	95

Figure 8. Substrate scope for enantioselective alkylation with diazo compounds. See SI for detailed conditions. The absolute configuration was assigned by the crystal structure of **5oa**.



(*R*)-**5ba**, 97% ee

(*R*)-**15**, 81% yield, 95% ee (4)

CONCLUSIONS

We here for the first time demonstrated that acceptor-substituted aryl azides and α-diazo carboxylic esters are suitable reagents for generating intermediate radicals for asymmetric photoredox reactions. These were exploited for the efficient visible-light-activated enantioselective α-alkylation and amination of 2-acyl imidazoles using a combination of a chiral rhodium-based Lewis acid catalyst and a photoredox sensitizer. Detailed mechanistic studies demonstrate that a radical process instead of a carbene/nitrene pathway is operative. Yields of up to 99% and enantioselectivities of up to 99.6% ee were achieved. Molecular nitrogen as the sole by-product, redox and proton neutral reaction conditions, as well as a broad compatibility with other functional groups render this transformation attractive. Further investigations on the development of novel reagents for asymmetric C-C/C-N bond formations are ongoing in our laboratory.

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Supporting Information

Synthetic details, details of mechanistic experiments, HPLC traces, NMR spectra, and crystallographic data (PDF)

X-ray crystal data of **Rh-enolate** (CIF)

X-ray crystal data of product **5oa** (CIF)

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