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Photoredox Catalysis of Intramolecular Cyclizations with a Reusable Silica-Bound Ruthenium Complex

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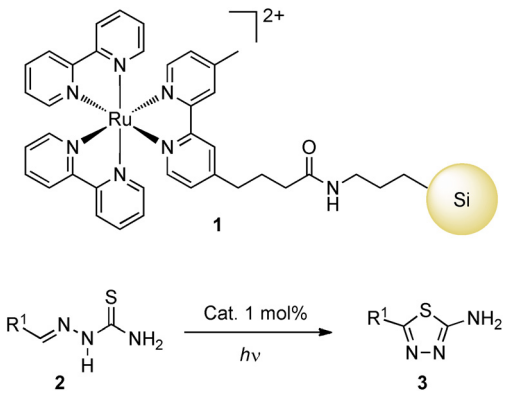
Photoredox catalysis with the use of a stable, reusable silica-bound chromophore was applied to the intramolecular cyclization of a series of 2-benzylidenehydrazinecarbothioamides to give 5-phenyl-1,3,4-thiadiazol-2-amines. The catalyst was readily prepared by carbodiimide-mediated coupling of commercially available amine-functionalized silica beads to a carboxylic acid functionalized ruthenium complex. The immobilized catalyst was readily removed from the reaction product by filtration and was used eight times without loss of catalytic activity. This simple, safe, and practical method is an attractive alternative to conventional procedures.

Light is an abundant and renewable resource in nature, and researchers have long sought to exploit its energy for chemical transformations.[1] Many organic molecules cannot absorb visible light efficiently, but photocatalysts such as $[Ru(bpy)_3]^{2+}$ (bpy = 2,2′-bipyridine) have been shown to drive the formation of new chemical bonds (C–C and C–hetero) for a wide range of organic transformations.[2]

To date, most visible-light-promoted photoredox catalysts are designed for homogenous use and the rare-earth-metal catalyst is unfortunately discarded during purification of the desired product. However, some heterogeneous CdS and TiO_2 materials[3] and metal–organic frameworks or organic polymers incorporating metal-complex chromophores[4] have recently been reported. Yoo and Kobayashi,[4h] for example, described an immobilized iridium-based catalyst for the aerobic phosphonylation of *N*-aryltetrahydroisoquinones under visible light. In this example, the polymer catalyst could be used at least four times without significant loss of activity. However, the methods by which these immobilized catalysts are prepared can sometimes be tedious, and hence, their widespread adoption by the chemistry community has been slow.[2c]

With this in mind, we sought to identify a simple process to covalently immobilize Ru^{II} polypyridyl complexes onto a silica platform to create stable, reusable photoredox catalysts for organic transformations. Ruthenium polypyridyl derivatives have previously been anchored to mesoporous silica for chemiluminescence detection[5] and photocatalytic hydrogen evolution,[6] but the synthetic pathways for preparing the immobilized complex were nontrivial, as they proceeded through multistep protocols involving silane derivatives of the bipyridine ligands. A more amenable synthetic approach has been devised by Papafotiou and co-workers,[7] who attached a biomimetic $[Ru(terpy)(bpy)_2](Cl)_2$ (terpy = 2,2′;6′,2″-terpyridine) complex to silica by aminopropyl functionalization of the silica surface, then amide coupling to a bipyridine carboxylic acid, and finally complexation with the ruthenium species. Herein, we report the most efficient route to date: a two-step process involving the direct immobilization of a carboxylic acid functionalized ruthenium(II) polypyridyl derivative onto a commercially available silica (SiliaBond Amine) to create a convenient, stable, and reusable photoredox catalyst (i.e., **1**) for organic transformations.

As proof of concept, we used the photoredox catalyst for intramolecular cyclizations of 2-benzylidenehydrazinecarbothioamides **2** to give 5-aryl-1,3,4-thiadiazol-2-amines **3** (Scheme 1). These and similar classes of heterocyclic molecules have received considerable attention owing to their wide range



Scheme 1. Photocatalytic reaction of 2-benzylidenehydrazinecarbothioamides to give 5-phenyl-1,3,4-thiadiazol-2-amines.

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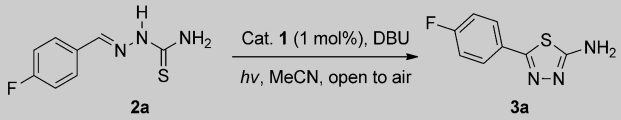
of pharmacological activity.[8] Whereas photoredox approaches have been outlined by Li and co-workers[9] for the cyclization of thioanilides to form the related 2-arylbenzothiazoles and by Yadav and Yadav[10] for the cyclization of acylhydrazones to form 1,3,4-oxadiazoles, these reactions were all performed under homogenous conditions. Herein, we report a readily prepared immobilized photocatalyst and its use to cyclize the more challenging amino-functionalized 2-benzylidene-hydrazinecarbothioamide substrates to form a family of 5-substituted-1,3,4-thiadiazol-2-amines with a range of inbuilt functional groups available for further reactions.

Table 1. Optimization of the reaction conditions.



2a 3a

Entry	Light source	Catalyst[a]	Conversion [%] (Yield [%])[b]
1	white light[c]	no catalyst	N.R.
2	dark	$[Ru(bpy)_3](PF_6)_2$	N.R.
3	white light[c]	$[Ru(bpy)_3](PF_6)_2$	<10
4	white light[c]	$[Ru(bpy)_3](PF_6)_2$[e]	<10
5	blue LED[d]	$[Ru(bpy)_3](PF_6)_2$	69 (63[f])
6	blue LED[d]	$[Ru(bpy)_3](PF_6)_2$[e]	(20[f])
7	blue LED[d]	$[Ru(bpy)_3](PF_6)_2$ (under N_2)	N.R.
8	blue LED[d]	**1**	72 (65[f])
9	blue LED[d]	**1** (under N_2)	N.R.

[a] Unless otherwise specified, a catalyst loading of 1 mol% was used. [b] Determined by HPLC. [c] A desk lamp (Nelson, 15 W) was used as the white-light source. N.R. = no reaction. [d] λ = 460–465 nm. [e] Catalyst: 5 mol%. [f] Yield of isolated product obtained after column chromatography. Substrate **2a** was synthesized according to a literature procedure.[12]

As this was the first application of photoredox catalysis for the preparation of phenylthiadiazolamines, we initially performed the reaction with substrate **2a** and $[Ru(bpy)_3](PF_6)_2$ under homogeneous conditions (Table 1). No reaction was observed in the absence of the catalyst (Table 1, entry 1) or in the presence of catalyst without light (Table 1, entry 2). The use of a standard white-light bulb as the initiator with a catalyst loading of 1 mol% gave only poor conversion over 24 h (Table 1, entry 3), and this yield was not significantly improved by increasing the catalyst loading to 5 mol% (Table 1, entry 4). The use of a monochromatic light-emitting diode (LED, 460–465 nm) with the catalyst (1 mol%) gave a much improved yield, and the complete consumption of **2a** was noted within 3 h (Table 1, entry 5). These mild, room-temperature conditions are superior to those involved in conventional protocols to access compounds such as **3a**, which typically involve elevated temperatures and $FeCl_3$ as a catalyst or acid chlorides.[8c,11] In an attempt to improve the reaction yield, the $[Ru(bpy)_3](PF_6)_2$ catalyst loading was increased to 5 mol%, but this resulted in precipitation of the catalyst together with the product as an opaque film in the reaction vessel, and no rate enhancement was observed (Table 1, entry 6).

The inorganic base K_2CO_3 has been used in similar photocatalytic reactions.[9] However, in the cyclization performed herein, only a trace amount of the product was formed, even if a large excess amount of this base was used.

Next, the heterogeneous reaction performed with the use of photocatalyst **1** was examined. The immobilized catalyst was easily prepared from two commercially available materials: aminopropyl-functionalized silica beads and the carboxylic acid derivative of $[Ru(bpy)_3]^{2+}$. A readily performed 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)-mediated amide coupling gave the complete catalyst. Despite being commercially available, to minimize cost the carboxylic acid derivative {i.e., $[Ru(bpy)_2(mba\text{-}bpy)](PF_6)_2$, mba-bpy = 4′-methyl-2,2′-bipyridine-4-butanoic acid} was synthesized by using well-established chemistry.[13]

Heterogeneous photocatalyst **1** (Table 1, entry 8) gave a yield of phenylthiadiazolamine **3a** similar to that obtained in the analogous homogeneous reaction (Table 1, entry 5) over the same timeframe. However, unlike $[Ru(bpy)_3](PF_6)_2$, immobilized catalyst **1** was conveniently collected from the product solution by means of vacuum filtration. After removal of the reaction solvent, the product was readily precipitated from water/ethanol in yields >50% (i.e., time-consuming column chromatography was no longer essential). We found that the catalyst collected in this simple manner could be used at least eight times for the intramolecular cyclization reaction with negligible loss of catalytic activity (Figure 1).

Li and co-workers[9] found that the presence of low levels of O_2 was critical for a successful photocatalyzed reaction. We

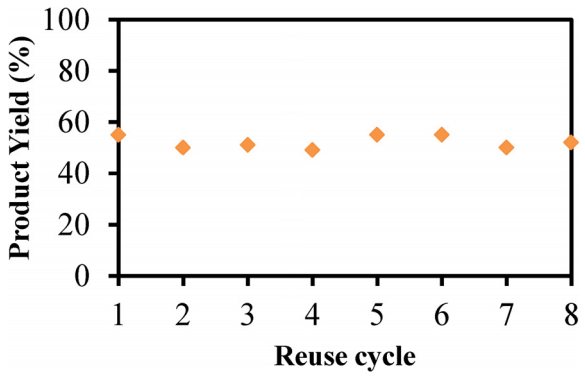
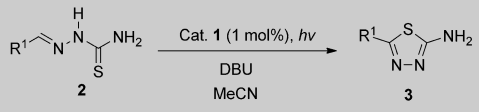


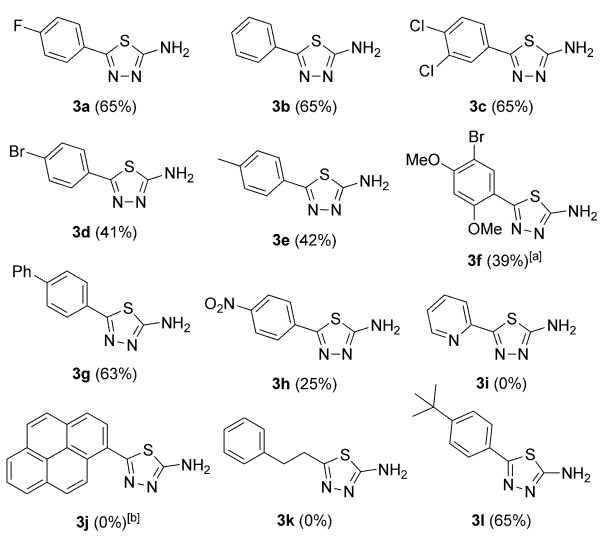
Figure 1. Product yields (using simple purification from ethanol/water solution) for the formation of **3a** upon recycling catalyst **1**. Prior to final purification, each filtered product solution was analyzed by photoluminescence and no emission at λ = 620 nm (characteristic of the Ru^{II} complex luminophore) was observed. Moreover, there was no change in the color of the catalyst with repeated use.

therefore examined our homogeneous and heterogeneous photocatalytic syntheses of phenylthiadiazolamines in the absence of oxygen (i.e., under an atmosphere of N_2; Table 1, entries 7 and 9) and no conversion to the desired product was observed. Indeed, optimum yields were obtained if the reactions were conducted with the reaction vessel open to the atmosphere.

To examine the scope of the reaction, a range of suitable substituted 2-benzylidenehydrazinecarbothioamides were subject to the reaction by using catalyst **1**. Most functional groups were well tolerated and gave clean conversions within 4–6 h to the cyclized products (Table 2), which included a number of novel products. Substrates with an unsubstituted (e.g., compound **2b**) or electron-deficient 4-fluoro- (e.g., compound **2a**) or 3,4-dichloro- (e.g., compound **2c**) substituted phenyl ring were cyclized in good yields of 65%. Moderate yields of 39–62% were obtained for substrates containing various other electron-donating and electron-withdrawing phenyl substituents (e.g., compounds **2d**–**g**). Low yields were obtained for the substrate with a 4-nitrophenyl substituent (e.g., compound **2h**). Upon adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the reaction mixture containing **2h**, the solution went dark brown, possibly reducing the quantity of light arriving at the catalyst. Attempts to cyclize substrates **2i**–**k** were not successful. Compounds **2f** and **2j** were not soluble in neat MeCN; thus, DMF and 30% DMF in MeCN were used, respectively.

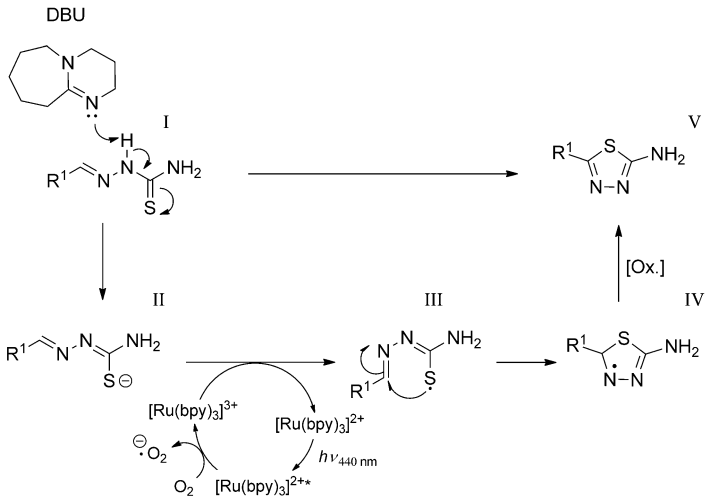
Table 2. Scope of the reaction by using the immobilized photocatalyst.





[a] Reaction was performed in 30% DMF in MeCN. [b] Reaction was performed in DMF.

Considering the critical dependence of these cyclization reactions on the photocatalyst, DBU, and O_2, a mechanism has been proposed involving 5-*endo-trig* cyclization.[9] First, the Schiff base is deprotonated to form the thiolate anion. Oxidation to the thiol radical is accomplished by the strong oxidant $[Ru(bpy)_3]^{3+}$ (or its immobilized analogue, Scheme 2) which is generated in situ upon quenching of the excited Ru^{II} species by O_2. Formation of the thiol radical in turn regenerates the Ru^{II} catalyst. The radical intramolecularly attacks the C=N bond in a 5-*endo-trig* cyclization to form intermediate **IV**. A hydrogen atom is lost to $O_2^{\cdot-}$ and **IV** regains aromaticity to give the desired product. Although a 5-*endo-trig* reaction is not favored by Baldwin's rules, exceptions involving small heterocyclic S-containing species are known.[14]



Scheme 2. Mechanism for the formation of 1,3,4-thioadiazoles.

DFT calculations support the proposed mechanism and experimental observations. The proton affinities of **2b**–**h**, **2j**, and **2l** are high (654–670 kJ mol^{-1} in MeCN solvent), which thus requires a strong base such as DBU (712 kJ mol^{-1} in MeCN) to ensure proton abstraction in the initial step (Scheme 2). The calculated oxidation of **II** by itself is endergonic by 450–474 kJ mol^{-1}, but inclusion of $[Ru(bpy)_3]^{2+}/[Ru(bpy)_3]^{3+}$ (−510 kJ mol^{-1}) makes this step favorable. Similarly, conversion of **III** into **IV** is unfavorable by approximately 100 kJ mol^{-1} without the inclusion of O_2^{-}/HO_2^{-} (−216 kJ mol^{-1}) in the calculation. Rearrangement of **III** into **IV** is exergonic, with calculated barriers of only 12–20 kJ mol^{-1}. The calculations support the observed dependence on the presence of the Ru photocatalyst, O_2, and strong base; O_2 is important both for the oxidation of **II** (O_2 is required to produce $[Ru(bpy)_3]^{3+}$ in the Ru redox cycle) and in the final step to remove a H atom from **IV** (as the O_2^{-} byproduct from the Ru redox cycle).

In conclusion, the utility of a readily prepared heterogeneous photoredox catalysis as a mild and selective method for radical initiation in the intramolecular cyclization of 5-aryl-1,3,4-thiadiazol-2-amines was demonstrated. The method is characterized by low catalyst loadings and simple reaction

design, and this enabled a wide range of 1,3,4-thiadiazoles to be readily accessed. The catalyst was exceedingly simple to prepare by using commercially available amine-functionalized silica. The immobilized catalyst was readily isolated from the reaction product by filtration and was used eight times with no loss in catalytic activity. This safe and practical method is an attractive choice if mild reaction conditions are required.

Experimental Section

Preparation of heterogeneous catalyst 1

The ruthenium complex {[Ru(bpy)$_2$(mba-bpy)](PF$_6$)$_2$} was prepared as previously described.[13] The complex (0.01 g, 0.01 mmol), EDCI (1 equiv.), and DMAP (0.3 equiv.) were dissolved in dichloromethane (10 mL). Predried SiliaBondAmine (0.1 g, 1.91 mmol g^{-1}; 40–63 μm 60 A, Silicycle, Inc., Canada, www.silcycle.com) was added to this solution, and the mixture was heated at reflux for 24 h under a nitrogen atmosphere. The red product was filtered in a sintered funnel; washed with dichloromethane, ethanol, methanol, and aqueous 2 M HCl; treated with saturated KPF$_6$; and washed with distilled water and finally acetone. The derivatized silica was then dried in vacuo at 70 °C overnight to give a bright orange granule powder (0.0033 mmol/100 mg). Control experiments with [Ru(bpy)$_3$](PF$_6$)$_2$ in the coupling step showed no attachment, as it was consequently washed out of the SiliabondAmine in the filtration step. Analysis by X-ray photoelectron spectroscopy and comparison of the as-received silica particles and the surface-grated material was consistent with successful ruthenium catalyst grafting.

Heterogeneous reaction conditions

A mixture of benzylidenehydrazinecarbothioamide (0.5 mmol), catalyst **1** (0.005 mmol, 1 mol%), and DBU (0.5 mmol, 1 equiv.) in MeCN (5 mL, unless stated otherwise) was placed at a distance of approximately 5 cm from a 10 W blue LED and was stirred at room temperature. Reactions were typically run for 4 h, at which point the LEDs were powered off. MeCN (5 mL) was added, and the mixture was sonicated (5 min). The mixture was filtered on a sintered funnel to remove the catalyst, and MeCN was removed under reduced pressure. The residue was diluted in ethanol (2 mL), cooled in ice, and water was added to give the desired 5-phenyl-1,3,4-thiadiazole-2-amine. The homogeneous reaction conditions are included in the Supporting Information.

Catalyst regeneration

Catalyst **1** was suspended in ethanol, sonicated (5 min), and filtered on a sintered funnel. The catalyst was further washed with 2 M HCl (2×5 mL) and distilled water and treated with a saturated KPF$_6$ solution to replace the counterion. A final wash with acetone was used to remove water, and the product was left to dry in vacuo at 60 °C overnight.

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Keywords: heterogeneous catalysis · photocatalysis · ruthenium · thiadiazolamines · visible light

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