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Visible-light enabled room-temperature dealkylative imidation of secondary and tertiary amines promoted by aerobic ruthenium catalysis†

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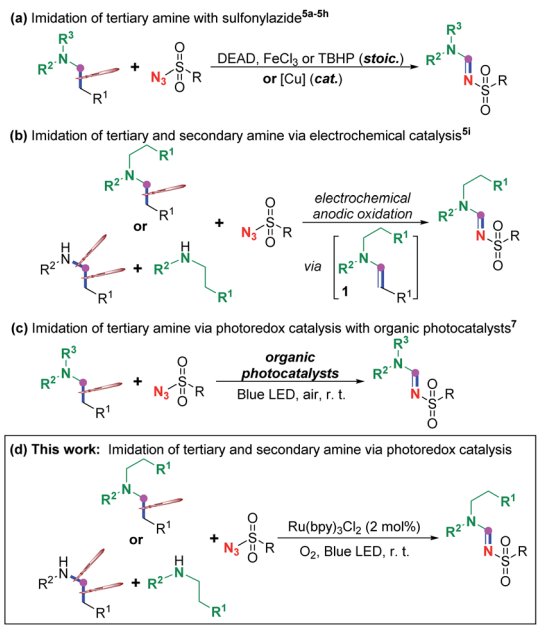
Employing sulfonyl azide as a nitrogen donor, a visible-light-enabled aerobic dealkylative imidation of tertiary and secondary amines involving C(sp^3)–C(sp^3) bond cleavage with moderate to excellent yields at room temperature is described. It has been demonstrated that this imidation could take place spontaneously upon visible-light irradiation, and could be facilitated considerably by a ruthenium photocatalyst and oxygen. An alternative mechanism to the previous aerobic photoredox pathway has also been proposed.

Introduction

Imine[1] and, particularly, amidine[2] are among the most ubiquitous and pivotal moieties in miscellaneous ligands, organocatalysts, functional materials, synthetic building blocks, bioactive molecules and pharmaceutics. Beside the most traditional approach through condensation between carbonyl and amine/amide to gain access to such significant scaffolds, various methodologies through transition-metal catalysed direct C–N cross-coupling of amine *via* C–H cleavage have been reported in the past decades.[3] Alternatively, it has also been widely reported that imine and imide could be acquired from azide instead of amine or amide.[4]

Among these methods with azide, imidation of the aliphatic chain of tertiary amine with sulfonyl azide through C(sp^3)–C(sp^3) bond cleavage (Scheme 1a)[5] has drawn our attention for C(sp^3)–C(sp^3) cleavage under mild conditions because it is generally challenging due to its high bond-dissociation energy and low polarity. In 2008, Li *et al.* disclosed a pioneering azo-mediated imidation of tertiary amines with sulfonyl azide at room temperature,[5a] followed by a couple of reports on the same transformation under mild conditions with other oxidants beside the azo compound, such as $FeCl_3$ (ref. 5*b*) and peroxides,[5c] or at high temperatures,[5d] while sulfamide could serve as a surrogate of sulfonyl azide in the presence of NBS[5e] or peroxide.[5f] Apart from these imidations through stoichiometric employment of oxidant, homogenous or heterogeneous copper-catalysed imidation of tertiary amine with sulfonyl azide has also been reported.[5g–j] Meanwhile, such imidation could not only be achieved with tertiary amine *via* C–C cleavage as illustrated above, it can also be realized on secondary amine involving C(sp^3)–N cleavage by electrochemical anodic oxidation (Scheme 1b),[5k] in which single electron transfer (SET) oxidation of tertiary or secondary amine to form nitrogen-centred radical cation has been proposed to initiate this imidation. Tertiary enamine **1** has been suggested to be the common intermediate for both tertiary and secondary amine, dividing the mechanism of these reaction into two processes:



Scheme 1 Imidation of amine with sulfonylazide.

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a dehydrogenation process to give this enamine intermediate, and a 1,3-dipolar cycloaddition-decomposition process to afford the final amidine product.[5]

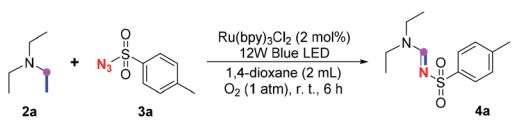
Our attention was then emphasized on other means beside electrochemical oxidation for the SET oxidation to generate nitrogen-centred radical cation that initiates such dealkylative imidation, and photoredox catalysis[6] which provides a potent synthetic strategy at room temperature and ambient pressure is considered to be the most efficient and green solution. Recently, Zeng[7a] and Pan[7b] disclosed two separate studies on visible-light-induced sulfonylimidation of tertiary amine using Eosin Y and acridinium salt, respectively, as organic photocatalysts in air (Scheme 1c),[7] based on an earlier report in which it had been proved that enamine **1** can be engendered from tertiary amine through photocatalysis.[8] However, employing secondary amine, such as diethylamine, instead of tertiary amine afforded sulfonylated diethylamine[7a] rather than the amidine product.[5k] Such sulfonyl azide participated imidation of secondary amine *via* photoredox catalysis is still unrealized.

Herein, as a continuation of our previous efforts on imidation[9] and other methodologies on the synthesis of nitrogen-containing compounds,[10] we would like to report our recent study on photoredox dealkylative imidation of tertiary and secondary amine with sulfonyl azide facilitated by aerobic ruthenium-catalysis to afford sulfonyl amidine at room temperature (Scheme 1d).

Results and discussions

Our investigation commenced with the optimization of the reaction conditions employing triethylamine (TEA, **2a**) as the tertiary amine substrate, as summarized in Table 1.

Table 1 Optimization of the reaction conditions[a]



Entry	Changes to standard conditions[a]	Yield[b] (%)
1	None	91
2	In EtOAc (2 mL)	25
3	In DCE (2 mL)	73
4	In DME (2 mL)	76
5	In THF (2 mL)	70
6	In toluene (2 mL)	32
7	In $MeNO_2$ (2 mL)	25
8	In H_2O (2 mL)	18
9	With $Ir(ppy)_3$ (2 mol%)	48
10	In open air	76
11	In Ar (1 atm)	49
12	No photocatalyst	29
13	No photocatalyst in Ar (1 atm)	27
14	No light	0

[a] Reaction conditions: TEA **2a** (0.5 mmol), TsN_3 (1.5 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol) in 1,4-dioxane (2 mL) at room temperature in O_2 (1 atm) under 12 W blue LED irradiation for 6 hours. [b] Isolated yields of **4a** based on **2a**.

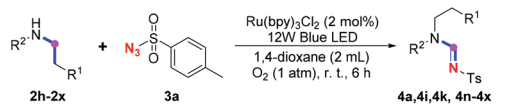
Table 2 Scope of the photoredox imidation of tertiary amine with azide[a]

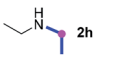
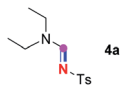
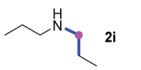
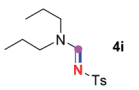
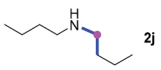
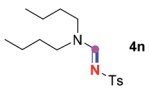
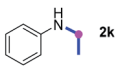
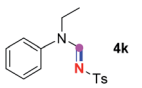
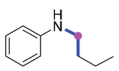
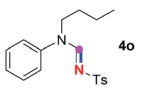
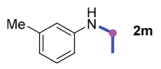
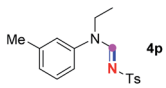
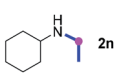
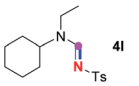
Entry	2	R	4	Yield[b] (%)
1	2a	Me (**3a**)	4a	91
2	2a	H (**3b**)	4b	80
3	2a	^{t}Bu (**3c**)	4c	86
4	2a	OMe (**3d**)	4d	67
5	2a	F (**3e**)	4e	97
6	2a	Cl (**3f**)	4f	82
7	2a	CF_3 (**3g**)	4g	90
8	2b	Me (**3a**)	4h	89
9	2c	Me (**3a**)	4i	85
10	2d	Me (**3a**)	4j	82
11	2e	Me (**3a**)	4k	48
12	2f	Me (**3a**)	4l	67
13	2g	Me (**3a**)	4m	70

[a] Reaction conditions: see entry 1, Table 1. [b] Isolated yields of **4** based on **2**.

When **2a** and tosyl azide (TsN_3, **3a**) was subjected to the photocatalyst $Ru(bpy)_3Cl_2$ in 1,4-dioxane under O_2 at room temperature, amidine **4a** was obtained in an excellent yield of 91% after 6 hours (entry 1). A series of widely used solvents were tested instead of 1,4-dioxane (entries 2–8), but none of them was found to provide **4a** in competent yields comparing to 1,4-dioxane. The yield of **4a** declined dramatically if the photocatalyst was replaced with $Ir(ppy)_3$ (entry 9). When the reaction was conducted in open air (entry 10), **4a** was acquired in a decreased yield of 76%, while the yield of **4a** further declined to 49% under argon (entry 11), demonstrating that the molecular oxygen could considerably promoted this imidation, although it is not prerequisite. Interestingly, the desired amidine product could still been generated, albeit in relatively low yields, in the absence of the photocatalyst either in O_2 (entry 12) or under argon (entry 13), whereas no **4a** was engendered in the absence of LED irradiation even with the photocatalyst and O_2 (entry 14), suggesting that this imidation with azide might spontaneously take place upon visible-light irradiation and neither photocatalyst nor molecular oxygen is prerequisite.

Table 3 Scope of the photoredox imidation of secondary amine with azide[a]



Entry	2	4	Yield[b] (%)
1			92
2			86
3			90
4			54
5			48
6[c]			61
7[c]			72

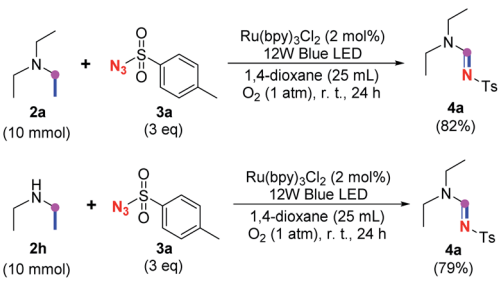
[a] Reaction conditions: see entry 1, Table 1. [b] Isolated yields of **4** according to their theoretical yields of 0.25 mmol from 0.5 mmol of **2h–2x**. [c] The reaction time was prolonged to 24 h.

Subsequently, the scope of amine **2** and sulfonyl azide **3** was explored, as shown in Table 2 and 3. With regard to the photoredox imidation of tertiary amine (Table 2), a series of benzenesulfonyl azides **3a–3g** with diverse *para*-substitutions on the benzene ring were tested under the optimized conditions (entries 1–7), and the excellent yields of corresponding amidines were generally maintained, except for amidine **4d** obtained from the electron-rich sulfonyl azide **3d** with strongly electron-donating methoxyl substituent. Reactions between other acyclic aliphatic tertiary amines and tosyl azide **3a** also provided amidines **4h–4j** in excellent yields, whereas dialkyl aniline **2e** afforded amidine **4k** in a moderate yield. In addition, two cyclic tertiary amines **2f** and **2g** could generate the desired product **4l** and **4m**, respectively, in synthetically acceptable yields.

Meanwhile, several secondary amines were investigated, as illustrated in Table 3. Since two molecules of secondary amine could provide only one molecule of the amidine product according to the mechanism proposed in previous work on the electrochemical imidation,[5k] the photoredox imidation of 0.5 mmol of the secondary amines could theoretically afford 0.25 mmol of corresponding amidines at most, and the yields in Table 3 were calculated accordingly. Results shown in Table 3 suggested that a series of secondary amines **2h–2n** were well tolerated with the optimized conditions established on tertiary amines, providing amidines **4a**, **4i**, **4k**, **4l** and **4n–4p** in moderate to excellent yields which are comparable to their tertiary amine siblings, although some of them required prolonged reaction time to guarantee the good yields. In addition, two gram-scale reactions with triethylamine (**2a**) and diethylamine (**2h**), respectively, under the optimized conditions have been conducted as shown in Scheme 2, and the good yields could be generally maintained.

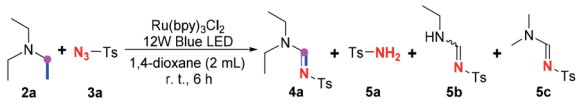
Furthermore, the spontaneity of this visible-light enabled imidation in the absence of oxygen and photocatalyst (entry 13, Table 1) attracted our attentions, for such observation suggested that an anaerobic pathways to realize this imidation probably coexist with the aerobic photoredox pathway proposed by Zeng and Pan,[7] where oxygen was proposed to serve a vital role in dehydrogenation. To gain more insights into the mechanistic picture, some control experiments were conducted, especially focusing on identification of byproducts generated along with the amidine product (Table 4).

It is discovered that sulfonamide **5a**, dealkylated[11] amidine **5b**, and amidine **5c** with an exchanged amino group[12] could be



Scheme 2 Gram scale reactions.

Table 4 Control experiments on tertiary amine **2a**[a]



Entry	O_2/Ar (1 atm)	[Ru] (mol%)	Yield[b] (%) 4a	5a	5b	5c
1	O_2	2	86	89	7	6
2	Ar	2	52	90	5	8
3	O_2	0	25	45	6	0
4	Ar	0	26	49	5	0
5[c]	O_2	2	0	0	0	0
6[d]	O_2	2	0	0	0	0
7[e]	O_2	2	0	0	0	0

[a] Reaction conditions: TEA **2a** (0.5 mmol), TsN_3 (1.5 mmol), $Ru(bpy)_3Cl_2$ (0.01 or 0 mmol) in 1,4-dioxane (2 mL) at room temperature in O_2 or argon (1 atm) under 12 W blue LED irradiation for 6 hours. [b] Isolated yields of **4a** and **5a–c** based on **2a**. [c] Without LED irradiation. [d] With TEMPO (2.5 mmol). [e] Without **2a**.

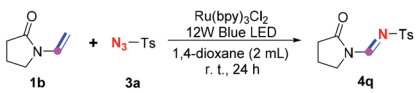
obtained under standard conditions (entry 1). However, when the imidation was conducted without oxygen, the yield of amidine **4a** dramatically declined, whereas the yields of all of the three byproducts **5a–c** generally maintained (entry 2). On the contrary, in the absence of the photocatalyst, **4a** and **5a** could only be acquired in very low yields regardless if the reactions were conducted in oxygen or argon, while no **5c** was obtained, suggesting that the ruthenium catalyst is crucial to the generation of these compounds. Furthermore, no amidine **4a** was engendered without visible-light irradiation (entry 5) or with TEMPO (entry 6), and neither were all of the three byproducts. A blank control experiment in the absence of amine **2a** also suggested that none of these byproducts were converted from the solvent, 1,4-dioxane (entry 7).

Previous studies on the imidation of amine with sulfonyl azide have almost reached a consensus that essential measures or reagents, such as heating, external oxidant, transition-metal catalyst, electrochemical anodic oxidation and/or photoredox process with photocatalyst, are necessary to the dehydrogenation of amine to form the transient enamine intermediate **1**.[5,7] Nevertheless, Zhu[13] has discovered that perfluoroalkanesulfonyl azide could readily decompose even at 0 °C in the presence of either tertiary or secondary amine *via* an intermolecular single electron transfer (SET) process between the azide and the amine, giving corresponding sulfonamide and *N*-substituted enamine equivalently. The formation of byproduct **5a**, therefore, suggested that, merely induced by visible-light irradiation at room temperature (entry 4, Table 4), a similar intermolecular SET process between sulfonylazide and amine could take place spontaneously without any photocatalyst and oxidant. It has also been demonstrated that such SET process can be facilitated by the ruthenium catalyst without oxygen, due to the amount of **5a** acquired in entry 2 that indicated most of **2a** could be converted to the enamine intermediate **1a** with the assistance of the ruthenium catalyst in the absence of oxygen. On the contrary, it seems that oxygen cannot promote the spontaneous formation of enamine **1a** (entry 3), and the previously proposed aerobic photocatalysis pathway[7] seems to contribute little in this ruthenium-promoted visible-light induced imidation, since the yield of **5a** indicated that most of **1a** was engendered through the above anaerobic SET process even in aerobic environment (entry 1). According to the above observations, it could be concluded that oxygen might be unnecessary to the conversion from amine **2a** to enamine **1a**, while it might enhance the following cycloaddition and ring-opening decomposition process, comparing the yields of **4a** in entries 1 and 2.

To better understand the roles of visible-light, oxygen and the photocatalyst in the subsequent 1,3-dipolar cycloaddition and instantaneous ring-opening process to give the final product, a series of control experiments using a less active but stable and commercially available *N*-substituted enamine **1b** as the substrate were performed (Table 5). Enamine **1b** was converted to corresponding amidine product **4q** in 31% yield under the standard conditions (entry 1), indicating that this visible-light enabled imidation is probably achieved through enamine intermediate as previous studies proposed.[5,7] The yield of **4q** significantly declined when this transformation took place in the absence of oxygen (entry 2), confirming the crucial role of oxygen in the cycloaddition and decomposition process which is suggested by the results of control experiments shown in Table 4. However, only trace amount of amidine **4q** could be observed on TLC when the reaction was conducted in the absence of the ruthenium photocatalyst or without visible-light irradiation (entries 3–6), demonstrating that the cycloaddition and decomposition process, although it might occur spontaneously with a extremely low rate (entry 6),[14] could be considerably facilitated by aerobic ruthenium photocatalysis (entry 1).

Beside the proposed aerobic photoredox mechanism,[7] a plausible alternative mechanism was therefore proposed according to the experimental observations discussed above and previously reported literatures.[5,7,13,14] This mechanism

Table 5 Control experiments on *N*-substituted enamine intermediate **1b**[a]



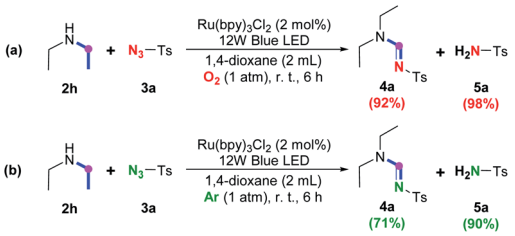
Entry	O_2/Ar (1 atm)	[Ru] (mol%)	LED irradiation	Yield[b] (%)
1	O_2	2	Yes	31
2	Ar	2	Yes	11
3	O_2	0	Yes	Trace
4	Ar	0	Yes	Trace
5	O_2	2	No	Trace
6	Ar	0	No	Trace

[a] Reaction conditions: **1b** (0.5 mmol), **3a** (1.5 mmol), $Ru(bpy)_3Cl_2$ (0.01 or 0 mmol) in 1,4-dioxane (2 mL) at room temperature in O_2 or argon (1 atm) under 12 W blue LED irradiation or in dark for 24 hours. [b] Isolated yields of **4q** based on **1b**.

comprises two processes: the anaerobic ruthenium-promoted photoredox SET dehydrogenation process to form enamine intermediate; and the cycloaddition and ring-opening decomposition process facilitated by aerobic ruthenium photocatalysis to afford the final amidine product (Scheme 3).

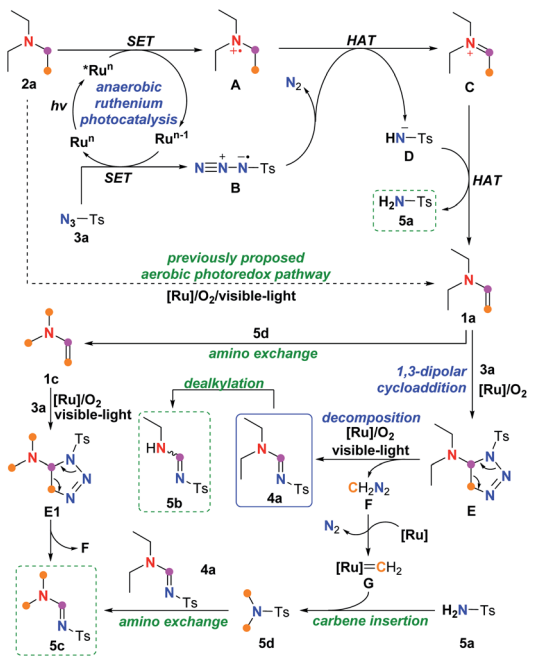
Initially, SET oxidation of amine **2a** by the excited state $*Ru^{n}$ produced *via* photoexcitation of the higher valent ruthenium catalyst forms tertiary amine radical cation **A**,[7] along with the reduced ruthenium species Ru^{n-1}, which undergoes another SET process with the azide TsN_3, giving azide radical anion **B**[5c,13] and closing the ruthenium catalytic cycle. In the absence of the ruthenium catalyst, the above SET process from amine **2a** to sulfonyl azide could take place spontaneously upon visible-light irradiation (entry 4, Table 4), albeit with lower efficiency, and such automatic SET process could also be realized at high reaction temperature[5c] or with perfluoroalkanesulfonyl azide.[13] Then, hydrogen atom transfer (HAT) from the amine radical cation **A** to the azide radical anion **B**,[13] along with the loss of N_2 from radical anion **B**, generates iminium **C**[7] and sulfonimide anion **D**[5c,13]. The iminium **C** would be deprotonated again by the sulfonimide anion **D** to provide the vital enamine intermediate **1a**, along with equivalent sulfonamide byproduct **5a**. Considering that approximately 90% of the starting amine **2a** was converted to **1a** and **5a** no matter if the reaction was conducted under aerobic or anaerobic conditions (entries 1 and 2, Table 4), the previously proposed aerobic photoredox pathway in which oxygen was required both in deprotonation of amine **2a** and in reoxidation of the organic photocatalysts,[7] might contribute little to this ruthenium-promoted visible-light enabled imidation.

Eventually, 1,3-dipolar addition of enamine **1a** with tosyl azide **3a** engenders a triazoline intermediate **E**, followed by decomposition of triazoline **E** to release diazomethane **F**,[14] along with the final amidine product **4a**, which might undergo oxidative dealkylation[11] to generated the de-ethylated byproduct **5b**. Results shown in Table 5 indicated that such cycloaddition-decomposition process, which might take place spontaneously albeit in very low efficiency (entry 6), could be promoted by aerobic ruthenium photocatalysis (entry 1). Additionally, in the presence of the ruthenium catalyst (entries 1 and 2, Table 4), diazomethane **F** could be converted to ruthenium carbene species **G**, which might be trapped by sulfonamide **5a** to form a *N*,*N*-dimethyl sulfonamide **5d** *via* N–H carbene insertion.[15] Amino group exchange[12d–f] between **5d** and the amidine product **4a** could directly afford the dimethyl amidine byproduct **5c**. Alternatively, such amino exchange might also take place on enamine **1a**,[12a–c] giving dimethyl enamine **1c** that also leads to **5c** through triazoline **E1** by cycloaddition–decomposition. The observation of byproduct **5c**, thus, could be considered as an indicator for the generation of diazomethane **F**.

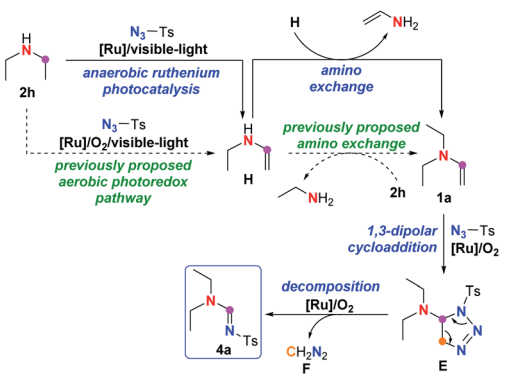


Scheme 4 Control experiments on secondary amine **2h**.

With regard to secondary amine, control experiments on amine **2h** (Scheme 4) suggested that almost all of the secondary amine could be efficiently dehydrogenated through the anaerobic ruthenium promoted photoredox SET process either in the presence (Scheme 4a) or in the absence (Scheme 4b) of oxygen, indicating that the previously proposed aerobic photoredox pathway[7] also contributes little to the conversion of secondary amine to give corresponding enamine. Meanwhile, the yield of **4a** is higher in the presence of oxygen (Scheme 4a), demonstrating the significance of oxygen to the following cycloaddition-decomposition process as observed in the imidation of tertiary amine.



Scheme 3 Plausible alternative mechanism for imidation of tertiary amine beside the aerobic photoredox pathway.



Scheme 5 Plausible mechanism for imidation of secondary amine.

The mechanism of imidation on secondary amine was therefore proposed as shown in Scheme 5. First, the secondary amine **2h** is converted to an enamine intermediate **H** through the same route proposed in Scheme 3. Unlike previous literature[5d,5k] in which the amino exchange between enamine **H** and amine **2h** was proposed to lead to the formation of enamine **1a**, it might be the amino exchange between two molecules of enamine **H** that is responsible for the generation of **1a**, since most of amine **2h** has been converted to enamine **H** either in aerobic or anaerobic environment according to the control experiments in Scheme 4, leaving little **2h** available for the following amino exchange. Finally, enamine **1a** undergoes the same cycloaddition-decomposition pathway shown in Scheme 3, leading to the amidine product **4a** though triazoline **E**, along with release of diazomethane **F**.

Conclusions

To summarize, a photo-induced and aerobic ruthenium-promoted dealkylative imidation of tertiary and secondary amine with sulfonyl azide through C(sp^3)–C(sp^3) bond cleavage at room temperature has been developed, providing a concise and efficient route toward the significant amidine scaffold under mild conditions. This protocol avoids the employment of metal complexes as the catalyst described previously,[5i] though both reactions could be realized at room temperature. To our knowledge, this is the first example for photocatalysed imidation of secondary amine with azide. Furthermore, unlike previously proposed mechanism for visible-light-induced imidation with nonmetal organic photocatalysts, a plausible mechanism for this ruthenium photocatalyst participated imidation, featuring the anaerobic ruthenium-promoted photoredox SET dehydrogenation of amine to form the key enamine intermediate and subsequent aerobic ruthenium photocatalysis facilitated cycloaddition-decomposition of this intermediate, have been proposed. Further studies to fully uncover the precise roles of visible-light, oxygen and photocatalyst, as well as application of this mild imidation to the preparation of amidine-based functional molecules, are undergoing.

Conflicts of interest

There are no conflicts to declare.

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