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Regioselective Ring-Opening Nucleophilic Addition of Aziridines through Photoredox Catalyst

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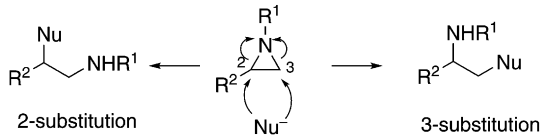
Abstract: A mild and efficient procedure was developed for the regioselective ring-opening nucleophilic addition reactions of aziridines *via* visible light photoredox catalysis, that provides a practical synthetic access to 1,2-bifunctional compounds. Furthermore, the regioselective synthesis of non-racemic amino ethers from chiral aziridine could also be achieved under mild conditions. Finally, a possible reaction mechanism was proposed and further supported by control experiments.

Keywords: aziridines; photoredox catalysis; regioselective ring opening; visible light

Aziridines are versatile substrates/building blocks for synthesis of numerous nitrogen-containing biologically compounds of contemporary interest.[1] Their ability to undergo ring-opening reactions owing to the strain inherent in the three-membered heterocycle and the electronegativity of the heteroatom contribute largely to their synthetic value in organic synthesis. In the past decades, extensive studies have been carried out on ring-opening reactions of aziridines with various nucleophiles,[2] among which most methods are mainly focused on catalytic process with Lewis acids[3] or Lewis bases,[4] transition metals[5] and fluoride ions.[6] Heteroatom-centered nucleophiles, such as chiefly alcohols, azides and halides have been devised for ring-opening addition of aziridines, and are of important interest because they provide a practical synthetic access to 1,2-bifunctional compounds containing amino ether, azido amine and β-halide amine functionalities, and the resulting compounds are found to be synthetically valuable in fundamentally important transformations.[7] However, when an aziridine is unsymmetrically substituted, two regioisomeric ring-opening products would be achieved



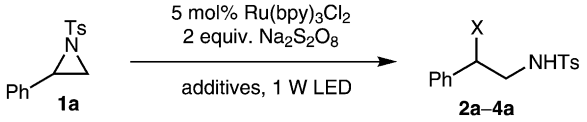
Scheme 1. Regioselectivity in the ring-opening processes.

(Scheme 1). The availability of a mild and efficient method thus remains appealing for the regioselective ring-opening reactions of aziridines. In this regard we considered that a photocatalytic process would potentially be suitable for the synthesis of 1,2-bifunctional compounds based on our continuing investigations on photoredox catalytic reactions.[8]

Nowadays, the use of visible light and a photoredox catalyst such as $[Ru(bpy)_3]Cl_2$ has appeared to offer very promising possibilities to activate molecules and promote synthetic transformations.[9] We envisioned that the amino radical cation generated from oxidative quenching process *via* visible-light photoredox catalysis[10] could lead to ring-opening nucleophilic addition reactions in which the nucleophiles and hydrogen atom would stem from reagent sources.

Considering that a judicious selection of the amine protecting group, which is adequately electron-withdrawing to suppress amine oxidation, could inhibit undesirable side reactions emerging from amine radical cation intermediates, our preliminary investigation was carried out on *N*-tosylaziridines (Table 1). First we began with the ring-opening reactions in polar protic solvents, such as MeOH. When *N*-tosylaziridine **1a** was treated with MeOH in the presence of 2 equiv. $Na_2S_2O_8$, as an effective oxidative quencher,[11] and 5 mol% $Ru(bpy)_3Cl_2$ under the irradiation of blue LED, we observed the corresponding ring-opening product – the 1,2-amino ether **2a**. The ring-opening reaction of **1a** with MeOH *via* visible-light photoredox catalysis was found to be highly regioselective and only the regioisomer derived from opening at the

Table 1. Visible light-induced ring-opening of **1a**.[a]



Entry	Additives	X	Time [h]	Yield[b] [%]
1	MeOH	OMe	1	**2a**, 86
2	LiBr, Hantzsch ester,[c] DMF	Br	3	**3a**, 86 (87:13)
3	NaN_3, Hantzsch ester,[c] DMF	N_3	5	**4a**, 90 (78:22)

[a] *Reaction conditions:* aziridine **1a** (0.1 mmol), $Na_2S_2O_8$ (2 equiv.), $Ru(bpy)_3Cl_2$ (5 mol%), additives and solvent (1 mL), irradiated under 1 W blue LED at room temperature.
[b] Isolated yield; the proportion of isomers given in parentheses was determined by ^1H NMR spectroscopy.
[c] Hantzsch ester = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

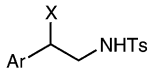
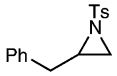
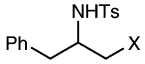
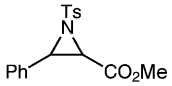
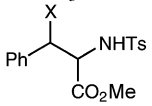
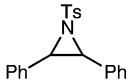
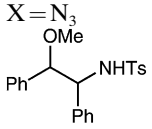
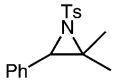
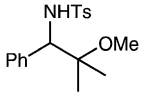
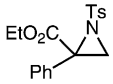
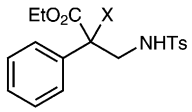
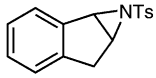
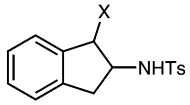
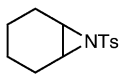
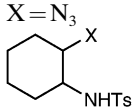
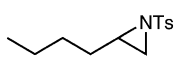
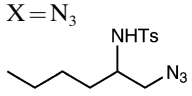
substituted carbon atom was observed. In this reaction, MeOH that served as a nucleophile could also be the hydrogen donor. Next, we examined other nucleophiles and chose aprotic solvents instead of MeOH. After a solvent and nucleophile screening, we found that when **1a** was reacted with 2 equiv. LiBr, 1.1 equiv. Hantzsch ester, 2 equiv. $Na_2S_2O_8$ and 5 mol% $Ru(bpy)_3Cl_2$ in DMF under the irradiation of blue LED, 2-bromo-2-phenylethanamine **3a** and 2-bromo-1-phenylethanamine were obtained in 86% yield with a ratio of 87:13. Under the same conditions, when LiBr was replaced by NaN_3, 2-azido-2-phenylethanamine **4a** and 2-azido-1-phenylethanamine were obtained in 90% yield with a ratio of 78:22. The results listed in Table 1 indicated the high regioselectivity of this protocol. Notably, for the reactions in aprotic solvents, for example, DMF, the Hantzsch ester was required to act as the hydrogen donor.[12] Furthermore, control experiments revealed that light and photocatalyst were both necessary for productive reactivity.

To demonstrate the general value of this strategy, a number of aziridines was prepared and submitted to the reaction conditions, and the results are summarized in Table 2. In all cases, the desired products were obtained in good yields with high regioselectivities. The phenyl groups substituted with electron-donating or electron-withdrawing groups did not affect the efficiency and the regioselectivity of the reactions (Table 2, entries 1–5). When the aromatic group was replaced by an alkyl one, the 2-amine compound was preferentially formed through terminal nucleophilic addition at the less hindered position (Table 2, entries 6 and 13). Moreover, the reaction was not limited to terminal aziridines, multisubstituted aziridines were also suitable substrates (Table 2, entries 7–10). Especially, for the aziridine **1i**, we achieved the ring opened product at the dimethyl-substituted carbon, which is mainly attributed to the stability of the carbocation. Cyclic *N*-tosylaziridines were also tolerated under the reaction conditions to afford the corresponding products in moderate to good yields (Table 2, entries 11 and 12). With respect to the regioselectivity observed in the reaction, we speculated that such a result might depend on the electronic effect (for instance, in the ring-opening of 2-arylaziridines) based upon the above results and the previous work from other groups,[1c] although most nucleophiles preferentially direct their attack to the site of lower substitution.

The scope of the protective groups on the amine was examined by treatment of aziridines **1a′**, **1a″** and **1a‴** under the same conditions. In comparison with the *N*-tosylaziridine, the reactions of the above three compounds were performed with lower efficiency. For example, except of 2-methoxy-1-amine **2a′**, neither the 2-bromo- nor the 2-azido-1-amine compound has been obtained in the reaction [Scheme 2, Eq. (1)]. In the cases of **1a″** and **1a‴**, only the nucleophilic addition with N_3^- was effective and led to 2-azido-1-amine compounds [Scheme 2, Eqs. (2) and (3)] in 82% and 67% yield respectively.

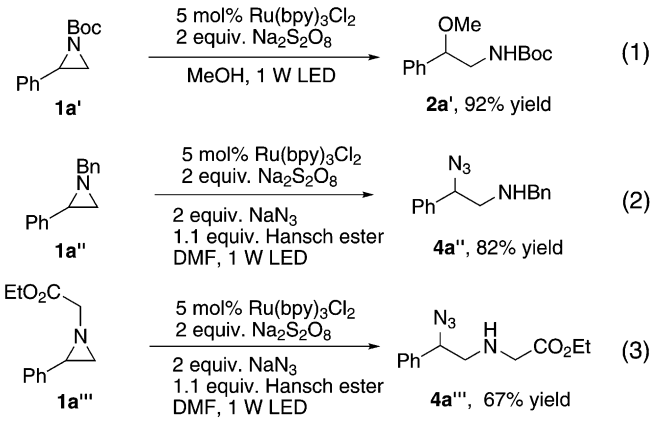
The reaction was also extended to the ring-opening of chiral aziridine (*S*)-**1a**. To our great pleasure, treatment of (*S*)-**1a** in MeOH led to an optically pure amino ether **2aa** in 87% *ee* (Table 3, entry 1). Such a result indicated an S_N2-type nucleophilic addition to the aziridine ring. Thus, we envisaged that a straightforward approach to the enantioselective synthesis of 1,2-amino esters could be achieved by performing the reaction in various alcohols *via* visible-light photoredox catalysis.[13] To demonstrate the general value of this strategy, an array of alcohols was investigated, and the results are summarized in Table 3. With less hindered alcohols, such as primary, allylic and propargylic alcohols, the corresponding products were obtained in good yields with high *ee* (Table 3, entries 1–3). A secondary alcohols (*i*-PrOH) was found to be less reactive and a reduced yield was observed (Table 3, entry 4). Under similar reaction conditions, the more sterically crowded *tert*-butyl alcohol failed to give any ring-opening product.

Table 2. Visible light-induced ring-opening of aziridines.[a]

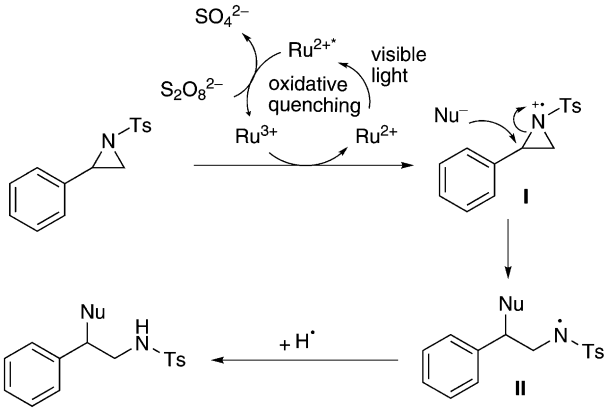
Entry	Substrates		Products		Time [h]	Yield[b] [%]
						
1	**1a**	Ar = Ph	**2a**	X = OMe	1	86
			3a	X = Br	3	86 (87:13)
			4a	X = N_3	5	90 (78:22)
2	**1b**	Ar = 4-$MeOC_6H_4$	**2b**	X = OMe	1	87
			3b	X = Br	3	74 (82:18)
			4b	X = N_3	5	90 (72:28)
3	**1c**	Ar = 4-FC_6H_4	**2c**	X = OMe	1	62
			3c	X = Br	3	65 (87:13)
			4c	X = N_3	5	72 (83:17)
4	**1d**	Ar = 3-$MeOC_6H_4$	**2d**	X = OMe	1	74
			3d	X = Br	3	78 (80:20)
			4d	X = N_3	5	80 (73:27)
5	**1e**	Ar = 2-ClC_6H_4	**2e**	X = OMe	1	90
			3e	X = Br	3	85 (83:17)
			4e	X = N_3	5	72 (86:14)
6						
	1f		**2f**	X = OMe	5	60
			4 f	X = N_3	7	82
7						
	1g		**2g**	X = OMe	3	76
			3g	X = Br	5	71
			4g	X = N_3	5	68
8	**1h**		**2h**		5	83
9	**1i**		**2i**		10	73
10						
	1j		**2j**	X = OMe	5	90
			3 j	X = Br	12	57
11						
	1k		**2k**	X = OMe	12	32
			4k	X = N_3	12	25
12						
	1l		**2l**	X = OMe	5	78
			3l	X = Br	12	85
			4l	X = N_3	7	88
13	**1m**		**4m**		3	71

[a] *Reaction conditions:* aziridine **1** (0.1 mmol), $Na_2S_2O_8$ (2 equiv.), $Ru(bpy)_3Cl_2$ (5 mol%), additives and solvent (1 mL), irradiated under blue LED at room temperature.

[b] Isolated yield; the proportion of isomers given in parentheses was determined by ^1H NMR spectroscopy.



Scheme 2. Ring-opening reactions of aziridines with different amine protecting groups.



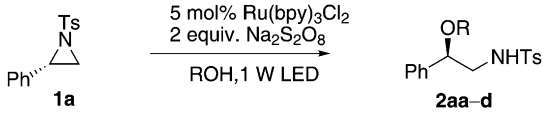
Scheme 4. Proposed mechanism.

The synthetic utility of the ring-opening products was exemplified by further transformations. Chemical modification of the azide functionality was studied using **4a** as the substrate (Scheme 3). Azido amine was easily converted to diamine **5a** by hydrogenation. Benzotriazole was readily obtained by the reaction of *in situ* generated benzyne with **6a** in 73% yield. Finally, as expected, **4a** was a suitable substrate for a Cu-catalyzed [3+2] alkyne/azide cycloaddition reaction to give compound **7a** in 70% yield.

Based upon the above results, a reaction mechanism was proposed as shown in Scheme 4. Under the irradiation of visible light, Ru(II) was converted to its excited-state Ru(II)*, which was then oxidatively quenched by $S_2O_8^{2-}$ to afford SO_4^{2-} and Ru(III), respectively. Sequential single-electron transfer from aziridine to Ru(III) served to form the amino radical cation intermediate **I** and regenerate catalyst Ru(II). Concerted ring-opening and nucleophilic addition afforded amino radical intermediate **II**, which was converted to the final product after abstraction of one hydrogen atom from MeOH or Hantzsch ester.

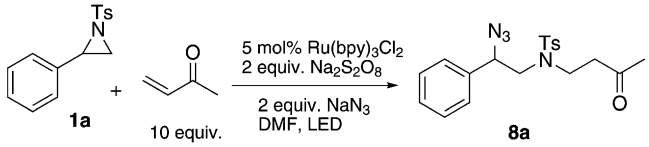
To add more credence of the existence of amino radical intermediate **II**, a control experiment was carried out with the addition of methyl vinyl ketone (MVK) as the radical scavenger. As expected, the Michael radical addition product **8a** was successfully obtained (Scheme 5).

Table 3. Visible light-induced regioselective nucleophilic ring-opening of (*S*)-**1a** with alclhols.[a]

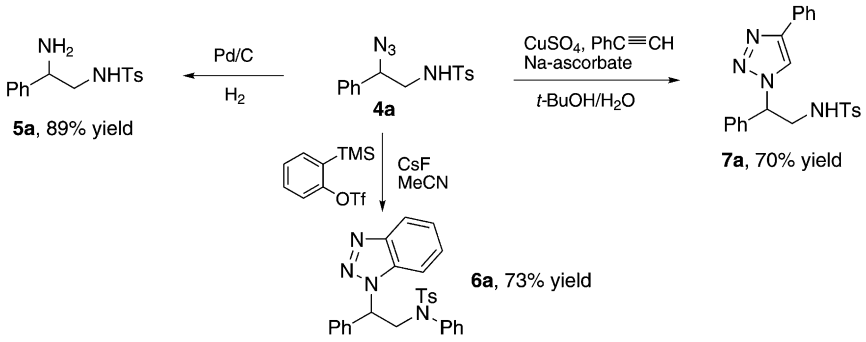


Entry	R	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	Me	2	**2aa**, 86	87
2	allyl	3	**2ab**, 78	83
3	propargyl	2	**2ac**, 94	67
4	*i*-Pr	4	**2ad**, 75	76

[a] In all the cases the alcohol served as the solvent.
[b] Isolated yield.
[c] Determined by chiral HPLC.



Scheme 5. Control experiment by reaction of **1a** with MVK.



Scheme 3. Transformation of the azide functionality in **4a**.

In conclusion, we have developed a mild and efficient protocol for the regioselective ring-opening nucleophilic addition of the *N*-tosylaziridines *via* visible light-induced photoredox catalysis. Moreover, the enantioselective sythesis of 1,2-amino esters also could be realized by an S_N2-type ring-opening reaction of optically pure aziridine with alcohols. Finally, further experiments provided a clear understanding of the reaction mechanism. Ongoing studies are focused on applying this reaction to more complex molecules.

Experimental Section

General Procedure

A 10-mL round-bottom flask was equipped with a magnetic stir bar and was charged with aziridine (0.1 mmol), $Na_2S_2O_8$ (47.6 mg, 0.2 mmol), $Ru(bpy)_3Cl_2$ (3.8 mg, 5 μmol), additives (LiBr or NaN_3, 2 equiv.; Hantzsch ester, 1.1 equiv.) and solvent (1 mL). The round-bottom flask was placed under blue LED irradiation and the mixture allowed to stir at room temperature for 1–12 h. Reaction progress was checked by thin layer chromatography (TLC). The reaction mixture was concentrated under vacuum, and ring opening products were purified by flash column chromatography.

Acknowledgements

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