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Photocatalytic intermolecular bromonitroalkylation of styrenes: synthesis of cyclopropylamine derivatives and their evaluation as LSD1 inhibitors†

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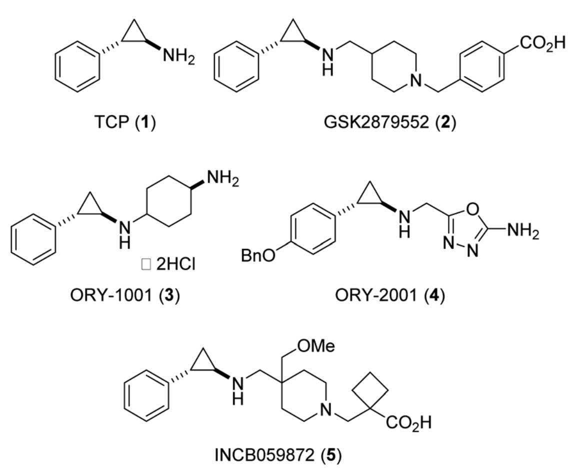
A mild and efficient method for photoredox-catalyzed bromonitroalkylation of alkenes is described herein. In this reaction, bromonitromethane serves as a source of both nitroalkyl and bromine for direct and regioselective formation of C–Br and C–C bonds from alkenes, and additional cyclization provides C–C bonds to the cyclopropylamine core as an LSD1 inhibitor.

Introduction

Lysine-specific histone demethylase 1A (LSD1, also known as KDM1A and AOF2) has an enzymatic function of removing a methyl group from the methylation site (Lysine 4 and 9) of histone H3.[1] Because this protein catalyzes FAD-dependent amine oxidation reactions, the methyl group of H3K4 me2 can be removed along with H3K4 me1 or H3K4 me0.[2] LSD1 has a regulatory function through demethylation of non-histone proteins such as P53, E2F1, and HIF1a, which are involved in tumor growth and the cell cycle.[3–5] Recently, there has been a report that LSD1 is closely related to cancer. LSD1 is overexpressed during human carcinogenesis and plays an important role in the staging of acute myeloid leukemia (AML) and small-cell lung cancer.[4,6,7] Thus, the inhibition of LSD1 has been in the spotlight in the development of anticancer agents. Various types of LDS1 inhibitors have been developed, and clinical studies targeting AML and small-cell lung cancer are in progress.[8] In particular, irreversible tranylcypromine (TCP)-based inhibitors (**1–5**) are currently being evaluated in various clinical trials and also being tested in combination with other therapeutic agents for diverse cancers and neurodegenerative diseases (Scheme 1).[9]

The general synthetic approach for TCP as an LSD1 core structure employs various cyclopropanation strategies:[10,11] cyclopropanation of styrene using diazo esters through carbenoids (Scheme 2(a1)),[12] dimethylsulfoxonium methylide (Corey–Chaykovsky reagent) generation (Scheme 2(a2)),[13,14] and Wadsworth–Emmons reaction with styrene epoxide (Scheme 2(a3)).[15–17] These protocols provide a predominant *trans*-adduct, and a subsequent Curtius rearrangement produces the cyclopropylamine. A recent addition to these methods is the Suzuki–Miyaura cross-coupling reaction of cyclopropylamine boronate (Scheme 2(a4)).[18] These protocols generally require 4–5-step sequences from their starting materials: ester to cyclopropylamine functionality (Scheme 2(a2): 4 steps) or epoxide from alkene to cyclopropylamine functionality (Scheme 2(a3): 5 steps).

Our synthetic scheme utilizes bromonitromethane, which serves as a Br and an alkyl radical source and as a carbenoid



Scheme 1 Known LSD1 inhibitors.

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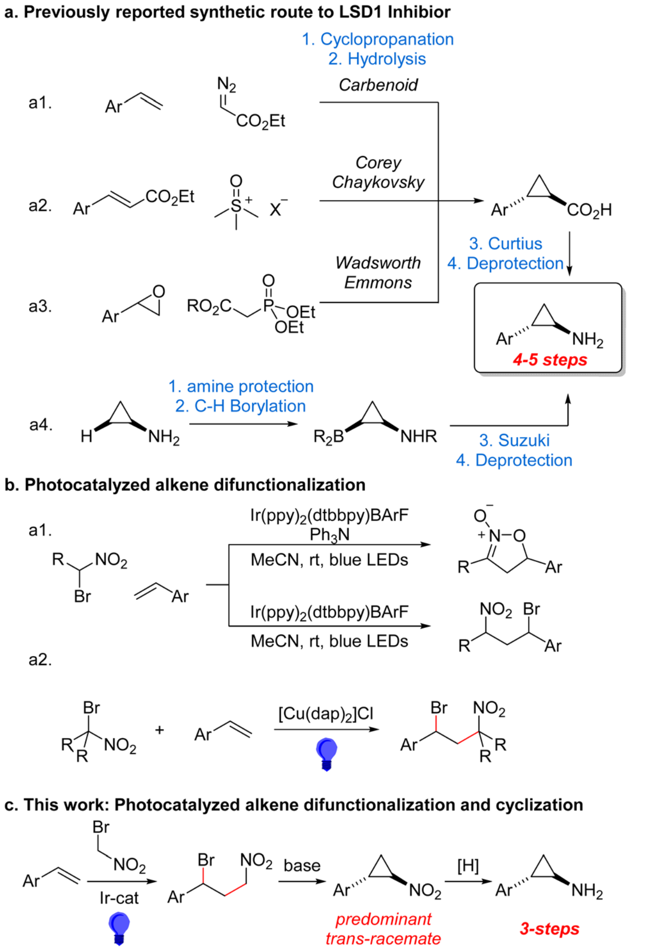


Scheme 2 Previously reported cyclopropane synthesis and photocatalytic approaches for aminocyclopropane.

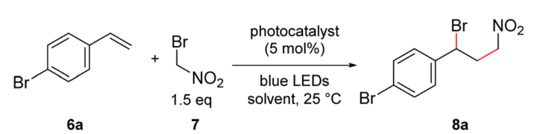
cyclopropanation precursor overall. To the best of our knowledge, only two reports exist regarding the addition of α-bromonitroalkanes to alkenes. A study by Ooi in 2020 showed a range of reactions of α-bromonitroalkanes toward styrenes to obtain to either isoxazoline-*N*-oxide or γ-bromonitroalkane (Scheme 2b).[19] Using Ir catalyst tuning, catalyst can control reaction pathway to access two distinct products. Additionally, they proposed nitroxyl radical intermediate **III** (see Scheme 5) based on the DFT calculation. More recently, the Cu(I)-catalyzed bromonitroalkylation of olefin has been reported (Scheme 2c).[20] Reiser and coworkers demonstrated the $[Cu(dap)_2]Cl$-catalyzed bromonitroalkylation of styrene and additional transformation to obtain nitrocyclopropane and aminocyclopropanes. Additionally, they elucidated the role of Cu catalysis in photoredox chemistry. In this study, we show a photoredox-catalyzed 1,3-difunctionalization of alkene to provide γ-bromonitroalkane adducts using Ir as the photocatalyst. Subsequent base-promoted cyclopropanation followed by reduction afforded aminocyclopropanes in three steps. Next, (sulfon)amidation reactions produced compounds **11** and **12** that share characteristic cyclcopropyl structures with LSD1 inhibitors (Scheme 2c).

Results and discussion

To determine the optimal catalyst, in our screening we utilized 4-bromostyrene (**6a**) and bromonitromethane (**7**) as model substrates in the presence of 5 mol% photocatalyst in 1,2 dichloroethane (DCE). A series of photocatalysts were found to afford the desired bromonitroalkylation adduct **8a** in low to moderate yields (Table 1, entries 1–5). It was found that *fac*-$Ir(ppy)_3$ provided the best yield (Table 1, entry 3). Unlike metal catalysts, organophotocatalysts did not promote the desired transformation (Table 1, entry 6). Other solvents such as CH_3CN and $CHCl_3$, rather than DCE, led to lower yields of **8a** (Table 1, entries 9 and 10), and virtually no reaction was observed when dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), or toluene was used as the solvent (Table 1, entries 11–13).

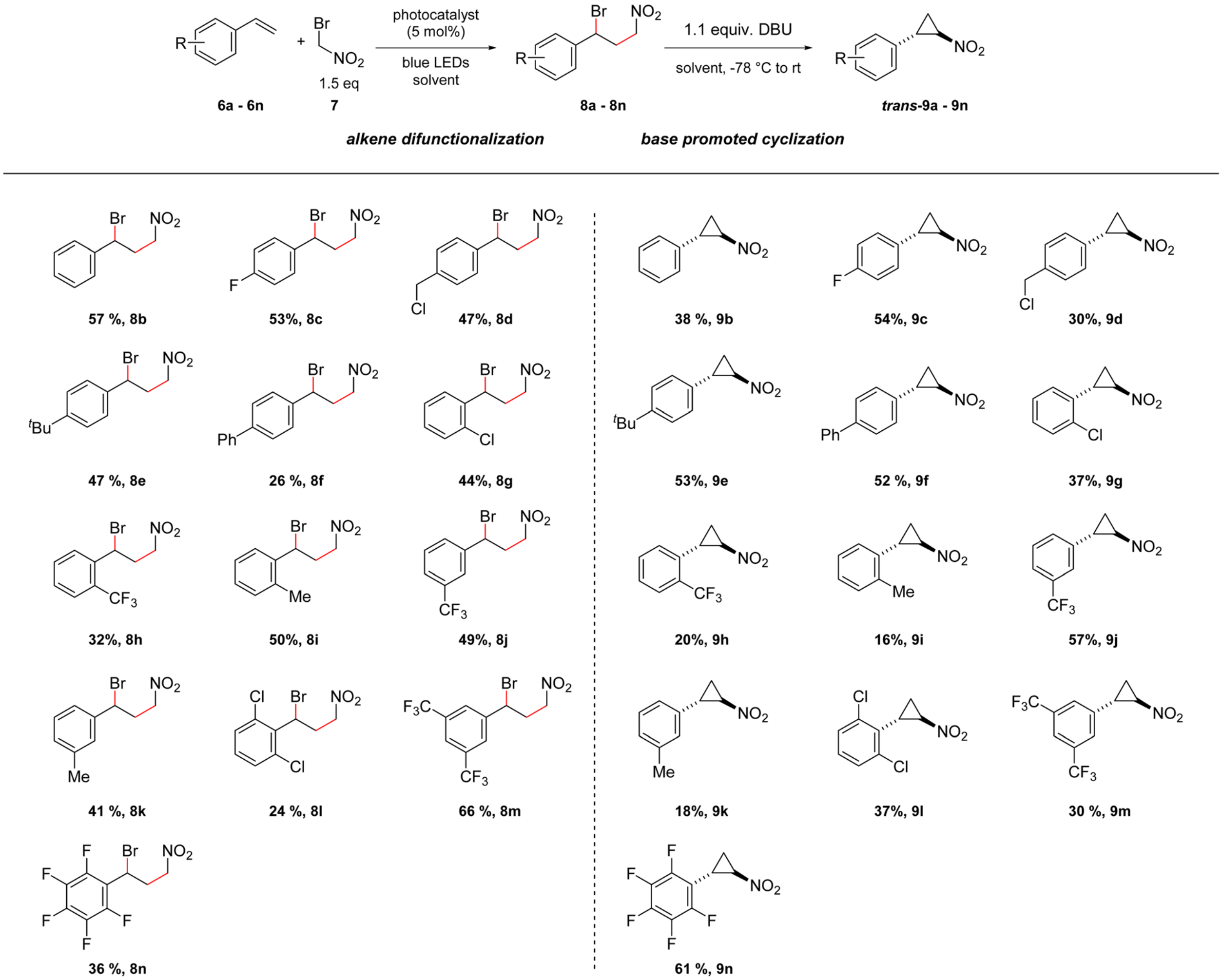
With the optimized reaction condition, the substrate scope was examined using various styrenes bearing different substituents on the aromatic ring (Scheme 3). The reactions of unsubstituted styrene (**8b**), 4-F (**8c**), 4-chloromethyl (**8d**), and 4-*t*-butyl-substituted styrene (**8e**) proceeded smoothly (57%, 53%, 47%, and 47% yields, respectively). However, 4-Ph-substituted styrene afforded a lower yield (26%, **8f**) than other *para*-substituted styrenes. Next, *ortho*-substituted substrates such as 2-Cl (**8g**), 2-CF_3 (**8h**), and 2-Me (**8i**) were subjected to the optimized reaction condition and provided moderate yields (44%, 32%, and 50%, respectively). The *meta*-substitution cases also afforded 3-CF_3 (**8j**) and 3-Me (**8k**) adducts with 49% and 41% yields, respectively. Finally, 2,6-Cl-substituted styrene (**8l**) gave a yield of 24%, and 3,5-CF_3 styrene (**8m**) and pentafluoro-substituted styrene (**8n**) afforded 66% and 36% yields, respectively. All the bromonitroalkylated adducts (**8**) were then treated with 1,8-

Table 1 Reaction optimization



Entry[a]	Photocatalyst (5 mol%)	Solvent	Yield[b] (%)
1	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	DCE	21
2	$Ru(Phen)_3\ PF_6$	DCE	23
3	***fac*-$Ir(ppy)_3$**	**DCE**	**47**
4	$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	DCE	12
5	$[Ir(dtbbpy)(ppy)_2]PF_6$	DCE	19
6	$[Acr^+{-}Mes][ClO_4^-]$	DCE	<5
7	$(Ir[dFppy]_2(bpy))PF_6$	DCE	10
8	$[Ir(C_{10}H_8N_2)(C_{11}H_8N)_2]PF_6$	DCE	33
9	*fac*-$Ir(ppy)_3$	CH_3CN	36
10	*fac*-$Ir(ppy)_3$	$CHCl_3$	33
11	*fac*-$Ir(ppy)_3$	DMF	<5
12	*fac*-$Ir(ppy)_3$	DMSO	<5
13	*fac*-$Ir(ppy)_3$	Toluene	<5

[a] All reactions were performed on a 0.25 mmol scale (0.1 M) and a standard reaction time of 18 h. [b] Isolated yield.



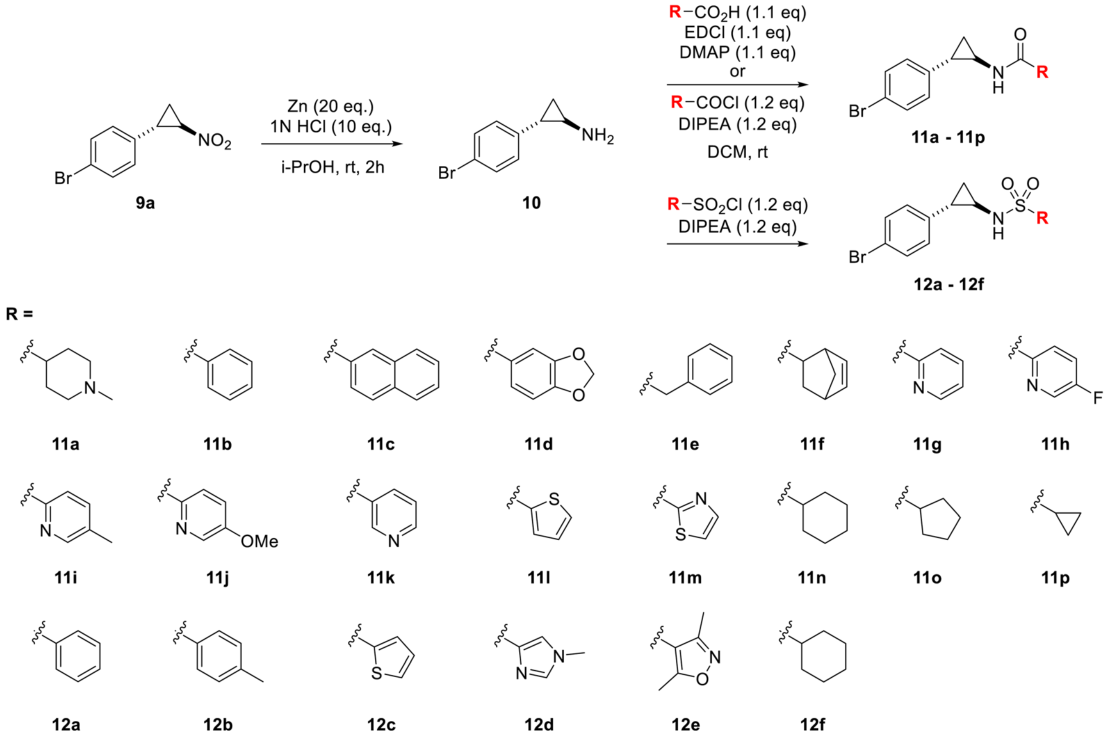
Scheme 3 Synthesis of a nitrocyclopropane scaffold *via* photocatalytic alkene difunctionalizaiton and cyclization.

diazabicyclo [5.4.0] undec-7-ene (DBU) to produce nitrocyclopropanes (**9**) by base-mediated cyclization (Scheme 3). Most *para*-substituted styrene-derived adducts showed fair yields. P–F (**9c**), *p*-tBu (**9e**), and *p*-Ph (**9f**) substituents showed better yields than the starting point, nonsubstituted phenyl (**9b**), while *p*-chloromethyl substituent (**9d**) did not. The *ortho*-substituted styrene series exhibited relatively low yields (**9h** and **9i**), except for the *o*-Cl substituent (**9g**), which afforded almost the same yield as **9b**. There appeared to be no clear electronic or steric effects of the *ortho*- and *para*-substituents on the reaction; nonetheless, the *meta*-substituents displayed a distinct electronic effect (**9j** *vs.* **9k**). Multihalogen-substituted styrene adducts also gave the corresponding nitrocyclopropanes in moderate yields, with the pentafluoro substituent being the best among them (**9n**).

With a series of nitrocyclopropanes, we next prepared grams of 4-bromobenzene-substituted nitrocyclopropane (**9a**). Nitro reduction using zinc powder and hydrochloric acid produced cyclopropylamine (**10**). Amidocyclopropanes **11** were easily obtained from carboxylic acids using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) as a coupling reagent or from acid chlorides. The installed acyl groups ranged from *N*-methylpiperidine (**11a**), benzyl (**11e**), aromatic carbocycles (**11b–11d**), and heterocycles (**11g–11m**) to cycloalkyl moieties (**11f**, **11n–11p**). We also synthesized sulfamoyl cyclopropanes (**12**) with sulfonyl chlorides and Hünig base (Scheme 4).

To determine the inhibitory activity of the compounds (**11** and **12**), we measured the relative inhibitory activity against human recombinant LSD1 at a concentration of 10 μM of the compounds; the corresponding results are presented in Fig. 1. The LSD1 inhibitor GSK2879552 was used as a positive control.

N-methylpiperidine containing **11a** showed slight LSD1 inhibitory activity compared to the control. Benzodioxole **11d** exhibited the best result among compounds bearing aromatic carbocycles. Benzyl compound **11e** showed activity similar to that of **11d**. Picolinamide **11g** showed ∼10% inhibition of LSD1 activity, and the introduction of an extra substituent on the pyridine ring (**11h–11j**) or altering the nitrogen position of the pyridine ring (**11k**) did not increase the LSD1 inhibitory activity.



Scheme 4 Synthesis of acyl and sulfamoyl variation of aminocyclopropane derivatives.

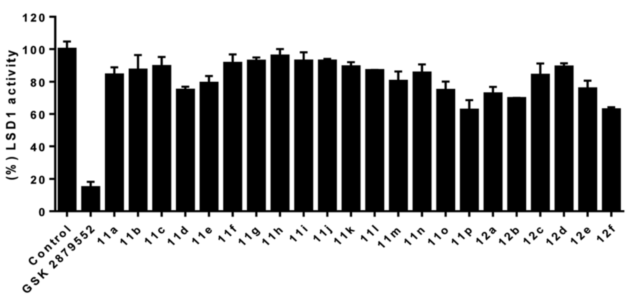
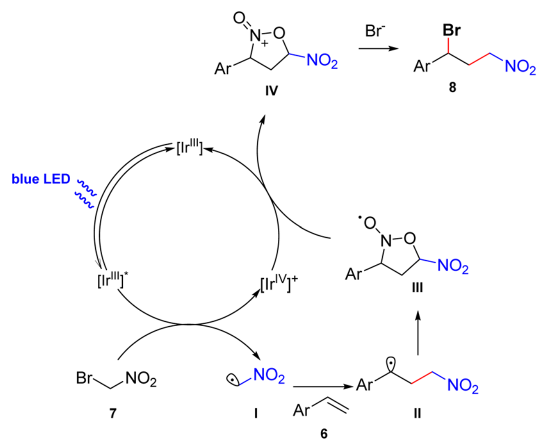


Fig. 1 Inhibition of LSD1 activity by compounds at a concentration of 10 μM. Activity percentage was determined following treatment with each test and reference compounds by the chemiluminescence assay method. Each data point is the average of three experiments (mean ± standard error of the mean). DMSO (1%) was used as the negative control.



Scheme 5 Plausible reaction mechanism.

Cyclopropyl **11p** exhibited ∼40% LSD inhibitory activity, which was the best among compounds **11.** Sulfamoyl cyclopropanes with aromatic carbocycles (**12a** and **12b**) were more advantageous than those comprising heterocycles (**12c–12e**). Cyclohexyl carboxamide **12f,** which resembles ORY-1001 (**3**), showed ∼40% inhibition, which was a level similar to that of cyclopropyl **11p**, confirming the potential of the cycloalkane R group.

A plausible reaction mechanism is proposed in Scheme 5 based on previous reports.[19] Irradiation of Ir(III) with visible-light gave the photoexcited state of the catalyst, which reduced bromonitromethane (**7**) to nitroalkyl radical **I** *via* a single-electron transfer (SET) process. Styrene **6** trapped radical **I** to generate benzylic radical **II,** which was further cyclized to give nitroxyl radical intermediate **III.** The intermediate **III** could then be oxidized to isoxazolinium intermediate **IV** and converted γ-bromo nitroadduct **8** by bromide ion.

Conclusions

We have developed a visible-light-photo-catalyzed reaction of bromonitromethane and various styrenes. This reaction provided bromonitroalkylated adducts, which could be further cyclized to access nitrocyclopropane derivatives. These nitrocyclopropanes served as the precursor of known LSD1 inhibitor *trans*-cyclopropylamines. Extensive right-side functionalization allowed us to identify novel scaffolds for LSD1 inhibitors. Further intensive medicinal chemistry efforts using this methodology will be presented in future reports.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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