RESEARCH ARTICLE doi.org/10.1002/adsc.70023

ADVANCED SYNTHESIS & CATALYSIS

Synthesis of Polycyclic Oxazolinium Compounds from Aryloxazolines and Alkynes *via* Dual Photoredox/Gold Catalysis and Rhodium Catalysis

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Manuscript received: April 7, 2025; Revised manuscript received: June 16, 2025;
Version of record online: August 21, 2025

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.70023

Abstract: A series of polycyclic oxazolinium compounds is synthesized from various aryloxazolines with silyl-substituted alkynes and internal alkynes *via* two synthetic pathways. By using dual photoredox/gold catalysis, the coupling of 2-aryloxazoline diazonium compounds with silyl-substituted alkynes affords silyl-substituted polycyclic oxazoliniums in 20%–36% yield. The coupling of 2-aryloxazolines with internal alkynes affords polycyclic oxazoliniums with up to 81% yield by Rh-catalyzed C─H bond functionalization. X-ray crystallographic analysis and circular dichroism reveal the successful coupling of chiral (*R*)-2-aryloxazolines with internal alkynes and affording the corresponding chiral (*R*)-oxazoliniums. Cytotoxicity analysis of the polycyclic oxazolinium compounds reveals cytotoxic activity on cancerous HeLa cells in micromolar dosage, with the lowest IC_{50} of 6.4 μM.

Keywords: chiral oxazolinium, dual photoredox/gold catalysis, oxazolines, polycyclic oxazolinium compounds, rhodium catalysis

1. Introduction

Oxazolinium, a class of cationic aromatic heterocycles bearing a quaternary bridgehead nitrogen, is electrophilic in nature and offers intriguing properties over oxazoline. Oxazolinium cations are useful intermediates in organic transformations, facilitating the synthesis of a wide range of compounds such as amides,[1] aldehydes,[2] and ketones.[3] It is noteworthy that the oxazolinium cations also known as key intermediates for substrate-assisted catalysis of *β*-*N*-acetylhexosaminidases (ENGases), a class of versatile biocatalysts for the production of *N*-linked glycopeptides and glycoproteins that are vital to human health and diseases.[4] In the past decade, the enhanced electrophilic properties of oxazolinium compared to oxazoline have been utilized to develop effective initiators and propagators for cationic ring-opening polymerization.[5] With the meticulous design of oxazolinium-based initiators,[6] the resulting biocompatible, heterotelechelic polymers with oxazolinium moiety end-group enable facile attachment of biomolecules and drugs that pave the way for the development of biomaterials and nanomedicine.[7]

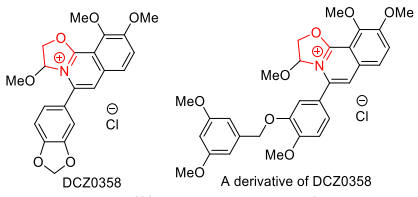
Notably, unlike the well-known nitrogen containing heterocycle templates for anticancer agents such as pyridine, pyrimidine, quinoline,[8] and oxazolinium derivatives have recently been found to exhibit antitumor activities. Shi and coworkers synthesized a polycyclic oxazolinium DCZ0358 which demonstrated potent anti-multiple myeloma activity *in vitro* and *in vivo* with IC_{50}: 10–18 μM.[9] A derivative of DCZ0358 was found

as a strong human carboxylesterase 2 (hCE2) inhibitor (IC_{50}: 1.19 μM), and molecular docking results demonstrated that the oxazolinium skeleton is crucial for its inhibitory activity (**Figure 1**).[10]

Given the vast utility of oxazoliniums in organic synthesis, biomaterials, and as a template with potential biomedical applications, it is important to enrich the variety of polycyclic oxazoliniums. However, the synthesis of polycyclic oxazolinium compounds such as DCZ0358 and its derivative required extensive synthetic effort and harsh reaction conditions that hindered the development of polycyclic oxazoliniums.[9,10] Therefore, it is important to develop efficient synthetic strategies to construct a diversity of polycyclic oxazoliniums in a modular approach under mild reaction conditions.

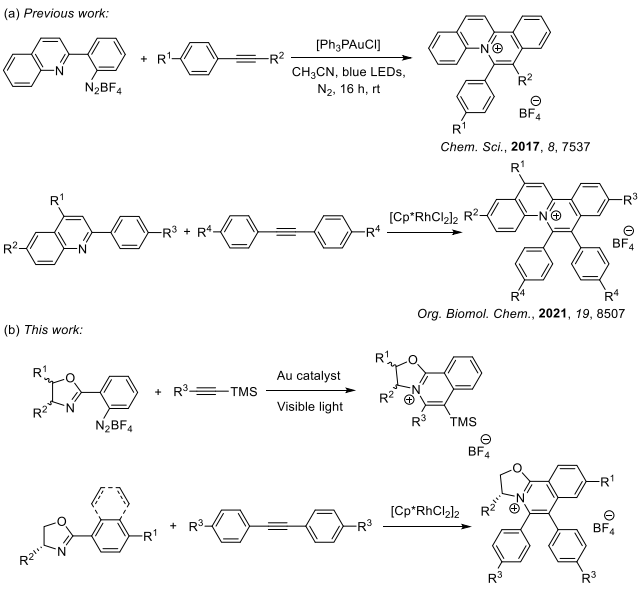
Dual photoredox/gold catalysis has emerged as a powerful tool for organic synthesis in recent years. As carbophilic Lewis acids, gold(I) and gold(III) species can activate unsaturated carbon–carbon bonds.[11] To overcome the intrinsic high redox potential of the Au(I)/Au(III) couple, visible light-mediated oxidation of Au(I) has become an alternative approach in which the use of external strong oxidants could be avoided.[12] The majority of reports employed dual photoredox/gold catalysis for the reaction of aryldiazonium salts with unsaturated compounds.[13] Previously, our group published a work in *cis*-difunctionalization of the alkyne *via* dual photoredox/gold catalysis for the synthesis of silyl-substituted quinolizinium from quinoline diazoniums and silyl-substituted alkynes.[14] However, employing oxazoline-substituted diazoniums in the dual photoredox/gold-catalyzed reaction remains unexplored. It is envisioned that the reaction of oxazoline-substituted diazoniums with silyl-substituted alkynes in dual photoredox/gold catalysis would give polycyclic oxazoliniums as the product.

In recent decades, transition metal (TM)-catalyzed C–H activation has been extensively adopted for the synthesis of polycyclic heterocyclic compounds.[15] Among various TM catalysts, Cp*Rh(III) complexes have been widely employed due to their high selectivity, unique reactivity, and broad functional group tolerance. A number of directing groups were developed for the construction of *N*-heterocycles.[16] However, studies adopting oxazoline as the directing group are limited. In 2013,



Cancer Lett, 2018, **421**, 135–144.; *RSC Adv*, 2019, **9**, 35904–35912

Figure 1. Representative chemical structures of bioactive polycyclic oxazolinium compounds.



Scheme 1. a) Synthesis of quinolizinium from aryl quinolines with silyl-substituted alkynes and internal alkynes. b) Synthesis of oxazoliniums *via* dual photoredox/gold catalysis and Rh(III)-catalyzed coupling of aryl oxazolines and alkynes.

Cheng's group reported the first example of polycyclic oxazolinium salt synthesized *via* Rh(III)-catalyzed C–H activation.[17] Recently, the groups of Cui and Chen reported Rh(III)-catalyzed tandem reactions involving annulation and nucleophilic ring opening for the synthesis of isoquinolone derivatives.[18] In their proposed reaction mechanism, oxazolinium salts are involved as the intermediates. In our previous study, Rh(III)-catalyzed coupling quinolines with internal alkyne yielded quinolizinium compounds.[19] However, the scope of the polycyclic oxazolinium compounds has not been studied and developed. To further explore the properties and potential applications of oxazolinium compounds in various fields, it is important to develop a series of polycyclic oxazolinium analogs.

Herein we report the synthesis of a series of polycyclic oxazolinium compounds *via* two methods: dual photoredox/gold catalysis and Rh(III)-catalyzed coupling of aryl oxazolines and alkynes (**Scheme 1**). X-ray crystallography analysis and circular dichroism (CD) collectively elucidated the successful formation of chiral polycyclic oxazoliniums from the corresponding chiral 2-aryloxazoline compounds. Cytotoxicity studies of the polycyclic oxazolinium compounds indicated remarkable structural tunability in cytotoxic activity on HeLa cells.

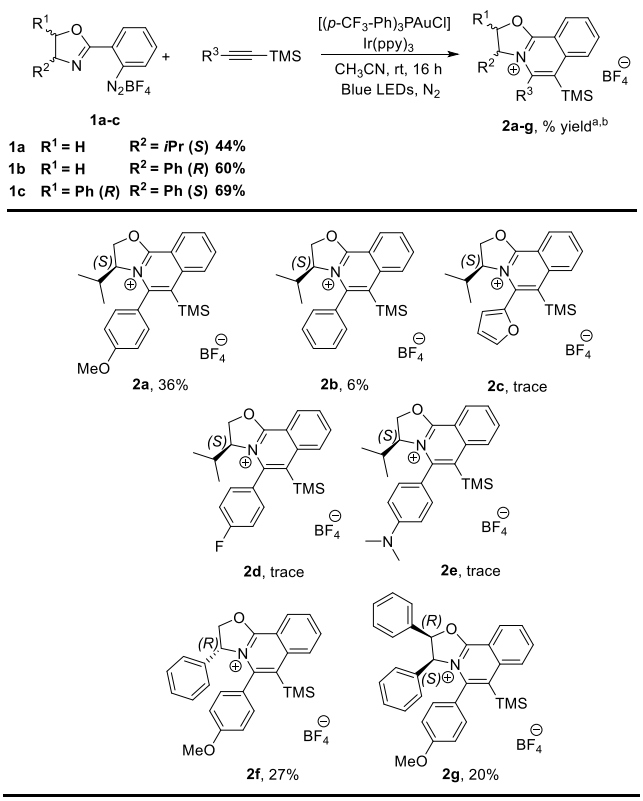
2. Results and Discussion

We initiated the synthesis of silyl-substituted oxazoliniums adapted from our previously reported dual photoredox/gold catalysis method, the conditions of photo reaction

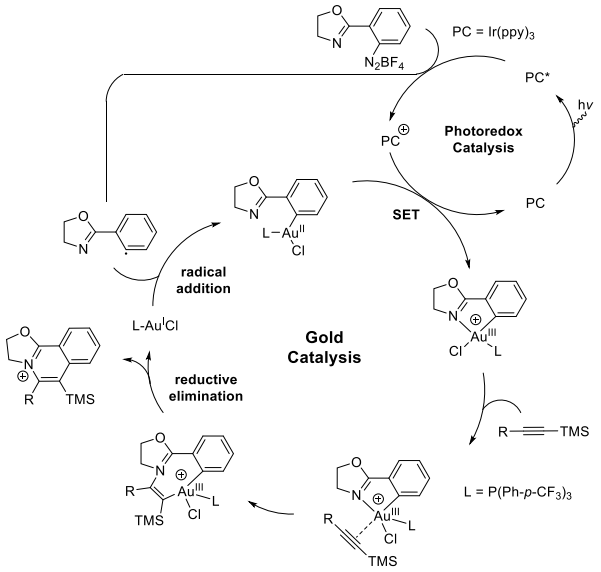
are performed under blue LEDs ($\lambda_{max} = 468$ nm) with a power of 32.9 W ($P = U \times I = 14.3\ V \times 2.3\ A$).[14] Different trimethylsilyl(TMS)-substituted alkynes (0.5 mmol) were reacted with 2-aryloxazoline *ortho*-diazonium **1a** (1.2 equiv.), [(*p*-CF_3-Ph)$_3$PAuCl] (10 mol %), Ir(ppy)$_3$ (1 mol %) in CH_3CN under nitrogen with blue LED irradiation at room temperature for 16 h (**Table 1**). The corresponding TMS-substituted oxazoliniums **2a** and **2b** were isolated with 36% yield and 6% yield, respectively. TMS-substituted alkynes bearing furan, fluorophenyl, and *N*,*N*-dimethylaniline groups gave a trace amount of product **2c-e**. Thus, (4-methoxyphenyl)ethynyl)trimethylsilane was selected to react with different diazoniums. Employing chiral 2-aryloxazoline *ortho*-diazoniums **1b** and **1c** gave TMS-substituted oxazolinium products **2f** and **2g** in 27% and 20% yield, respectively.

Based on the above experimental results and literature findings,[14,20] a plausible reaction mechanism of dual photoredox/gold catalysis is proposed and shown in **Scheme 2**. Under irradiation, the photocatalyst Ir(ppy)$_3$ is first excited to facilitate the formation of an aryl radical,

Table 1. Scope of TMS-substituted oxazoliniums *via* dual photoredox/gold catalysis.



[a] Reaction conditions: TMS-substituted alkynes (0.5 mmol, 1 equiv.), **1a-c** (0.6 mmol, 1.2 equiv.), [(*p*-CF_3-Ph)$_3$PAuCl] (10 mol %), and Ir(ppy)$_3$ (1 mol %) in CH_3CN (5 mL) under N_2 and blue LEDs ($\lambda_{max} = 468$ nm) at room temperature for 16 h; [b] Isolated yield.

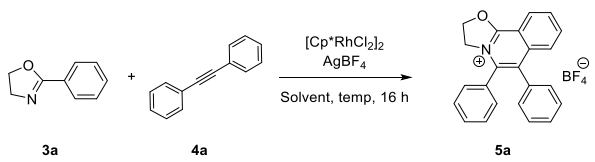


Scheme 2. Proposed reaction mechanism of dual photoredox/gold catalysis.

followed by radical addition with the Au(I) catalyst [(*p*-CF_3-Ph)$_3$PAuCl] to generate the Au(II) species, and subsequently oxidized by single electron transfer from the photocatalyst to form the Au(III) intermediate. The Au(III) intermediate is coordinated with the TMS-substituted alkynes and undergoes reductive elimination to give the corresponding TMS-substituted oxazoliniums.

To further expand the scope of polycyclic oxazoliniums, we then studied the reaction conditions with [Cp*$RhCl_2$]$_2$ for C–H activation of aromatic-substituted oxazolines. 2-Phenyloxazoline **3a** (0.1 mmol) and diphenylacetylene **4a** (1.5 equiv.) were employed as the substrates with different amounts of [Cp*$RhCl_2$]$_2$ catalysts (1–8 mol%), $AgBF_4$ (2 equiv.) in DCE (2 mL) for 16 h at 60 °C. Using 5 mol% of catalyst gave a higher yield of **5a** with 45% yield (**Table 2**, entries 1-3). No product formation was observed when no catalyst or silver salt was used, indicating that the [Cp*$RhCl_2$]$_2$ and $AgBF_4$ play a crucial role in this transformation (entries 4-5). Decreasing the silver salt loading (entry 6) or varying the reaction temperature (entries 7-8) showed no significant change in product yield. The reaction was then screened with different solvents (entries 9-15). The highest product yield of 66% was observed with CH_3OH and 2,2,2-trifluoroethanol (TFE) as the solvents (entries 9-10). Tetrahydrofuran (THF) gave a moderate yield (49%, entry 11). Lower yields were afforded when the reaction was conducted in acetonitrile, toluene, ethanol, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (entries 10-15). Furthermore, it is important to enhance the solubility of oxazolines, especially polycyclic oxazolines such as naphthalene-substituted oxazolines, to ensure an optimized solvent system for the reaction, with the concern of easy accessibility and operation cost. Since DCE

Table 2. Optimization of reaction conditions for the synthesis of oxazolinium **5a** *via* Rh(III)-catalysis.



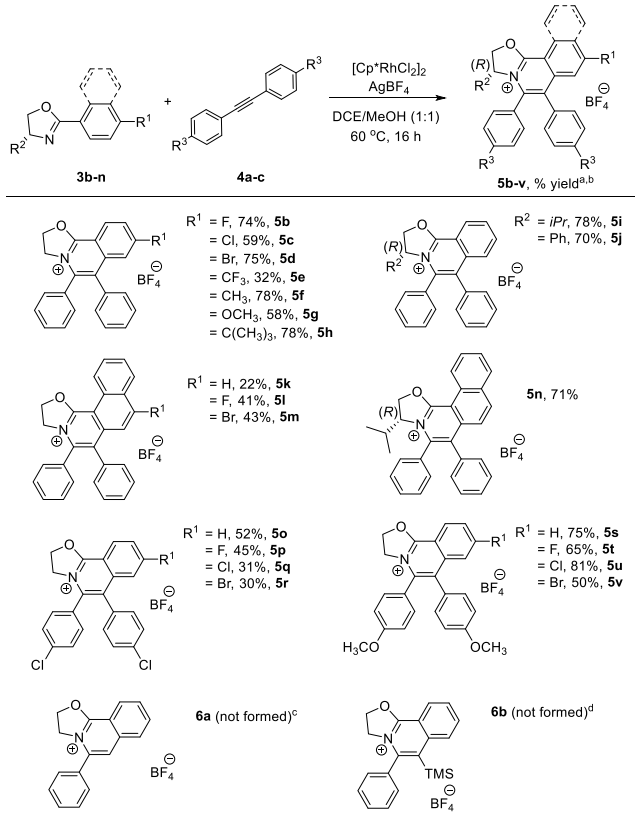
Entry[a]	$[Cp^*RhCl_2]_2$ [mol %]	$AgBF_4$ [equiv.]	T [°C]	Solvent [mL]	% yield[b]
1	1	2	60	DCE	18
2	5	2	60	DCE	45
3	8	2	60	DCE	39
4	0	2	60	DCE	0
5	5	0	60	DCE	0
6	5	1	60	DCE	32
7	5	2	25	DCE	34
8	5	2	100	DCE	38
9	5	2	60	CH_3OH	66
10	5	2	60	TFE	66
11	5	2	60	THF	49
12	5	2	60	CH_3CN	12
13	5	2	60	Toluene	0
14	5	2	60	C_2H_5OH	31
15	5	2	60	HFIP	0
16	5	2	60	DCE/CH_3OH (1:1)	59

[a] Reaction conditions: 2-phenyl-2-oxazoline **3a** (0.1 mmol), diphenylacetylene **4a** (0.15 mmol, 1.5 equiv.), $AgBF_4$, and $[Cp^*RhCl_2]_2$ in solvent (2 mL) at different temperature for 16 h; [b] Isolated yield.

possesses the highest solubility of naphthalene at 57 °C,[21] a solvent system of DCE/CH_3OH (1:1) was used to afford a comparable product yield of 59% (entry 16), which was then used as the optimized reaction conditions.

With the optimized reaction conditions, we then explored the scope of the reaction by using various 2-aryloxazolines (0.5 mmol) and diphenylacetylene **4a** (1.5 equiv.) as substrates. 2-Aryloxazolines **3b-h** bearing halogen, alkyl, and ether as substituents were well tolerated with the reactions giving polycyclic oxazolinium products **5b-h** with 32%-78% yield (**Table 3**). Increasing the steric bulkiness of 2-aryloxazolines with chiral isopropyl **3i** or phenyl-substituted oxazoline **3j** showed excellent tolerance and afforded products **5i** and **5j** in 78% and 70% yield, respectively. Employing 2-(naphthalen-1-yl)-oxazolines **3k-m** reduced the formation of oxazolinium products **5k-m** in 22%–43% yield. Interestingly, employing chiral isopropyl-substituted 2-(naphthalen-1-yl)-oxazoline **3n** gave higher product formation of **5n** in 71% yield, which may be attributed to the stabilization of the oxazolinium cations from the electron-donating isopropyl substituent. Further expansion of the scope employing electron-withdrawing disubstituted bis(*p*-chlorophenyl)acetylene **4b** with 2-aryloxazolines **3a-d** giving products **5o-r** in 30%–52%

Table 3. Substrate scope of oxazolinium compounds *via* Rh(III)-catalysis.

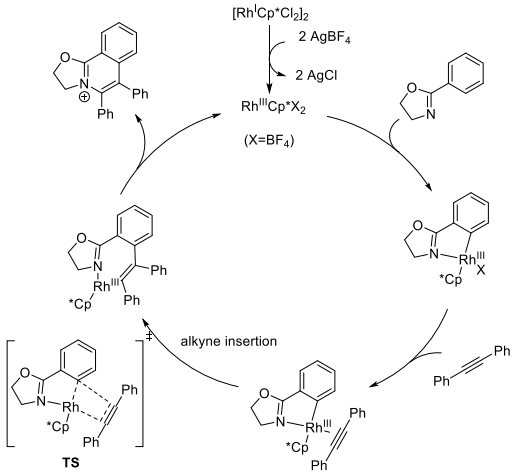


[a] Reaction conditions: 2-aryloxazoline (0.5 mmol, 1 equiv.), diarylacetylene (1.5 equiv.), $AgBF_4$ (2 equiv.), and $[Cp^*RhCl_2]_2$ (5 mol %) in DCE/CH_3OH (10 mL, v/v 1:1) at 60 °C for 16 h; [b] Isolated yield; [c] Reaction with phenylacetylene; [d] Reaction with 1-(trimethylsilyl)-2-phenylacetylene.

yield. In contrast, employing electron-donating disubstituted bis(*p*-methoxyphenyl)acetylene **4c** with 2-aryloxazolines **3a-d** giving products **5s-v** with higher yields (50%–81% yield) when compared to the electron-withdrawing disubstituted analogs. Employing phenylacetylene and 1-(trimethylsilyl)-2-phenylacetylene gave no desired product **6a-b**, suggesting that the reaction was chemoselective towards diphenylacetylenes.

Based on the above experimental results and literature reports,[18,22] a plausible reaction mechanism of Rh(III)-catalysis is proposed and shown in **Scheme 3**. The rhodium catalyst is first activated to Rh(III) species by $AgBF_4$, followed by C–H activation of the phenyl oxazoline by the Rh(III) species to give a five-membered rhoda-cycle. Coordination of alkyne to the Rh and subsequent alkyne insertion form a seven-membered rhoda-cycle. Reductive elimination of the Rh(III) species releases the oxazolinium, and the Rh(I) species is then oxidized to Rh(III) for the next catalytic cycle.

The molecular structure of polycyclic oxazoliniums was confirmed by ^1H NMR, ^{13}C NMR, and HRMS.



Scheme 3. Proposed reaction mechanism of Rh(III)-catalysis.

Notably, a crystal structure obtained by X-ray crystallography analysis revealed the structure of (*R*)-oxazolinium **5i**, bearing a polycyclic oxazolinum cation with tetrafluoroborate (BF_4^-) as the counterion (**Figure 2**a and **Table S1-S2**, Supporting Information). CD confirmed that the stereochemical properties of (*R*)-**5i** and (*R*)-**5j** are retained from the corresponding chiral 2-aryloxazolines (*R*)-**3i** and (*R*)-**3j** (**Figure** 2b and Supporting Information). To our knowledge, we are the first to synthesize chiral polycyclic oxazolinium compounds from chiral 2-aryloxazolines, which can be readily prepared from commercially available chiral amino alcohols.

After synthesizing the new polycyclic oxazolinium compounds, we moved on to explore their biological activity against cancer cells. HeLa cells were incubated in various concentrations of polycyclic oxazoliniums **5a-v** for 24 h and subjected to a cytotoxicity study to determine their inhibitory concentration (IC_{50}). Importantly, all oxazoliniums exerted cytotoxicity towards HeLa cells in the micromolar dosage, and no cytotoxicity was observed in 2-aryloxazolines **3a** and **3b** (**Figure 3** and Supporting Information). Oxazoliniums **5a-f** exerted fair cytotoxicity (IC_{50}: 53.1–89.5 μM), which indicated a limited effect of 2-aryloxazolines R^1 substituents bearing halogens or the methyl group. 2-Aryloxazolines bearing R^1 substituents with electron-donating ether **5g** and *tert*-butyl **5h** significantly improved its cytotoxicity (IC_{50}: 33.7 and 11.1 μM, respectively). Aryloxazolines bearing R^2 substituents with isopropyl **5i** or phenyl **5j** exhibited a more profound cytotoxic property (IC_{50}: 7.8 and 12.2 μM, respectively). Oxazolinium **5k**, **5L**, and **5m** with naphthalene moiety significantly improved its cytotoxicity (IC_{50}: 10.8, 12.2, and 24.2 μM, respectively) compared with their corresponding phenyl analogs **5a**, **5b**, and **5d** (IC_{50}: 62.2, 89.5, and 55.4 μM, respectively).[23] Interestingly, oxazolinium **5n** containing both an electron-donating isopropyl on an oxazoline ring and a naphthalene moiety exhibited the highest cytotoxicity (IC_{50}: 6.4 μM). Oxazoliniums

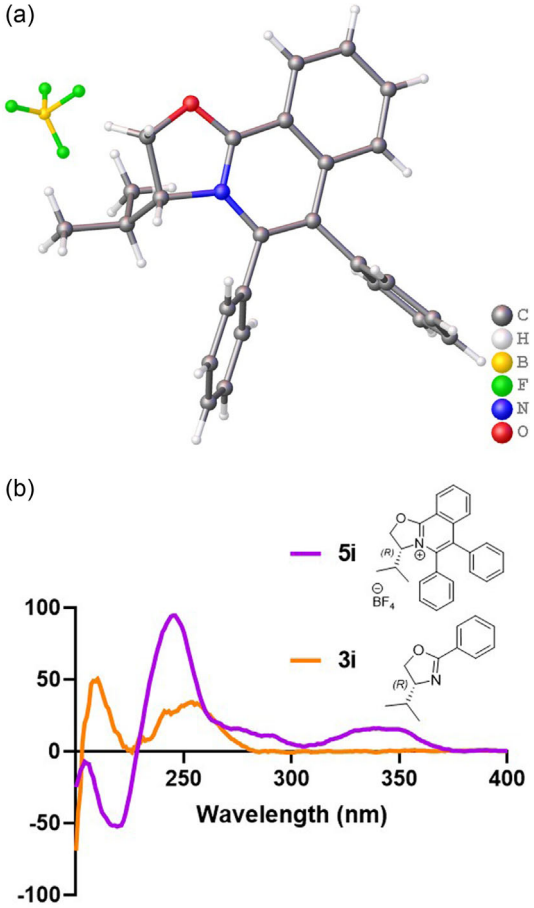


Figure 2. a) X-ray crystallography of chiral oxazolinium (*R*)-**5i**. b) CD spectra of chiral oxazolinium (*R*)-**5i** and chiral 2-aryloxazoline (*R*)-**3i** (Concentrations of (*R*)-**5i** and (*R*)-**3i** are 0.1 mg mL^{-1} in CH_3CN).

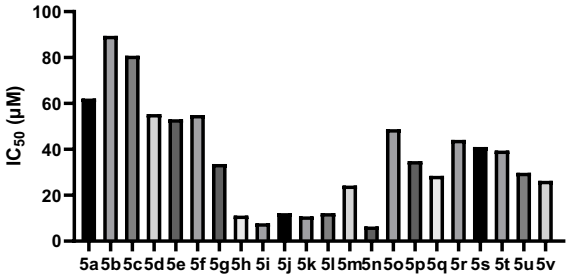


Figure 3. IC_{50} values of polycyclic oxazolinium compounds on HeLa cells.

with either electron-withdrawing R^3 substituents **5o-r** or electron-donating R^3 substituents **5s-v** on the diphenyl moiety were both conferred with increased cytotoxicity (IC_{50}: 26.3–48.8 μM) compared with their corresponding analogs **5a-d** (IC_{50}: 55.4–89.5 μM). Notably, these results demonstrated that the polycyclic oxazolinium compounds could be a potential scaffold for cancer therapy, and shed

some light on the oxazolinium structure-cytotoxicity relationship that can be instrumental for anticancer drug discovery.

3. Conclusion

In summary, we have developed a series of polycyclic oxazolinium compounds from aryl oxazolines and alkynes *via* dual photoredox/gold catalysis and rhodium catalysis. Expansion of the substrate scope indicated that aryl oxazolines were compatible with various alkynes with up to 81% yield of oxazolinium products. Notably, our modular approaches enable the convenient preparation of chiral oxazolinium compounds from chiral 2-aryloxazolines, which can be readily prepared from commercially available chiral amino alcohols. Cytotoxicity study revealed the cytotoxic activity of oxazolinium compounds on HeLa cells in micromolar dosage. We envision that this work would facilitate the application of oxaozlinium compounds in different research areas.

4. Experimental Section

CCDC 2 434 661 contains the supporting crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.UK/structures.

*General Procedure for Synthesis of 2-Aryloxazoline Ortho-Diazoniums **1a-c**:* A mixture of amino benzonitrile (10 mmol, 1 equiv.), chiral amino alcohol (15 mmol, 1.5 equiv.) and anhydrous $ZnCl_2$ (0.5 equiv. or 3 equiv.) in 6 mL of chlorobenzene was refluxed at 160 °C under N_2 for 24 h. After purification by column chromatography on silica gel using EtOAc/hexane as eluents to obtain the desired products **a1-c1**. 2-(*o*-Aminophenyl)oxazolines **a1-c1** (4 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (20 mL) under N_2 and cooled to 0 °C. Boron trifluoride diethyl etherate $BF_3{\cdot}Et_2O$ (8 mmol, 2 equiv.) followed by *tert*-butyl nitrite (^{t}BuONO) (8 mmol, 2 equiv.) were then added dropwise into the reaction mixture. After stirring at room temperature for 1 h, the solvent was evaporated, and the residue was redissolved in a minimum amount of CH_3OH. Diethyl ether was then added until a white or yellow precipitate formed. The solid was filtered and vacuum dried to obtain the desired products **1a-c**.

*General Procedure for Synthesis of TMS-Substituted Oxazoliniums **2a-g**:* A mixture of oxazoline diazonium salt (0.6 mmol, 1.2 equiv.), TMS-substituted alkyne (0.5 mmol, 1 equiv.), [$(p$-CF_3-$Ph)_3PAuCl$] (10 mol %), $Ir(ppy)_3$ (1 mol %) and 5 mL of CH_3CN was added into a 20 mL test tube. The test tube capped with a rubber septum was evacuated and refilled with nitrogen three times. The tube with the reaction mixture was then irradiated with blue LEDs for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/acetone as eluent to give the desired products **2a-g**.

*General Procedure for Synthesis of 2-Aryloxazolines **3a-m**:* Synthesis of 2-aryloxazolines **3a-h, n**: A mixture of benzonitrile (10 mmol, 1 equiv.), aminol alcohol (15 mmol, 1.5 equiv.) with $ZnCl_2$ (5 mmol, 0.5 equiv.) in 6 mL of chlorobenzene was heated at 160 °C for 24 h. The reaction was monitored by TLC analysis until all starting materials were consumed. After completion, the reaction mixture was purified by flash column chromatography using EtOAc/hexane as eluent to give the desired products **3a-h, n**. Synthesis of 2-aryloxazolines **3i-m**: Acyl chloride (10 mmol, 1 equiv.) in 10 mL of dry CH_2Cl_2 was added dropwise into a 100 mL round bottom flask equipped with aryl amino alcohol (11 mmol, 1.1 equiv.) in 40 mL of dry CH_2Cl_2 and 10 mL of TEA at 0 °C. After addition, the reaction mixture was warmed to ambient temperature, TsCl (11 mmol, 1.1 equiv.) and 5 mL of TEA were then added, and the resulting mixture was heated at 80 °C for 16 h. The reaction was monitored by TLC analysis until all starting materials were consumed. After the reaction, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography using EtOAc/hexane as eluent to give the 2-aryloxazolines **3i-m**.

*General Procedure for Synthesis of Oxazoliniums **5a-v**:* A mixture of 2-aryloxazolines **3a-n** (0.5 mmol, 1 equiv.), diarylacetylenes **4a-c** (0.75 mmol, 1.5 equiv.), [Cp*$RhCl_2$] (5 mol %), $AgBF_4$ (1 mmol, 2 equiv.) in DCE/CH_3OH (10 mL, *v*/*v* 1:1) was heated at 60 °C for 16 h. The reaction was monitored by TLC analysis until all starting materials were consumed. The reaction mixture was purified by flash column chromatography using CH_2Cl_2/CH_3OH as eluent to give the desired products **5a-v**.

*Cytotoxicity Analysis of Polycyclic Oxazolinium Compounds **5a-v**:* The cytotoxicity of polycyclic oxazolinium compounds **5a-v** on HeLa cells was determined with the MTS assay. HeLa cells (5,000 cells) were first seeded into a 96-well plate and allowed to adhere for 24 h before they were incubated with various concentrations of oxazolinium (diluted from the stock solution in DMSO to 0.2, 2, 10, 20, 50, 100, and 200 μM) in Dulbecco's Modified Eagle's Medium (Gibco) supplemented, 10% *v*/*v* Fetal Bovine Serum (Gibco), and 100 U/ml penicillin (Gibco), 100 ug/ml streptomycin (Gibco) for another 24 h 37 °C with 5% CO_2. After the incubation period, the culture medium was filled with 20 μL of MTS solution (CellTiter 96 AQueous one solution cell proliferation assay, Promega Corporation Cat.# G4000), and incubated for 1 h at 37 °C with 5% CO_2. The optical density of the formazan solution at a wavelength of 490 nm was determined with a Ledetect 96 LED based eight channel microplate absorbance reader, and at least three replicated wells were examined for each concentration. GraphPad Prism was used to calculate the IC_{50} values.

Acknowledgements

The authors gratefully acknowledge the financial support by the Research Grants Council of the Hong Kong Special Administrative Region, China (no. PolyU15300520), PolyU Postdoc Matching Fund Scheme (no. P0043412: W262), the State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University (no. P0053072: ZZV2), the University Research Facility in Life Sciences (ULS), and the University Research Facility in Chemical and Environmental Analysis (UCEA) of PolyU. We would like to thank Prof. F. K.-C. Leung for hardware support of in vitro experiments.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available in the Supporting Information of this article.

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