Visible Light-Mediated [2+2]-Cycloadditions for the Formation of Macrocyclic Dimers

Cody H. Ng†, Scott L. Kim†, Ilia Kevlishvili§, Gianmarco Terrones§, Emily R. Wearing†, Heather J. Kulik§*, Corinna S. Schindler†*

†Department of Chemistry, University of Michigan, 930 N University Ave, Ann Arbor, MI 48109, United States
§Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139, United States

ABSTRACT: Macro cyclic, dimeric lactones have known pharmacological activities that make them attractive synthetic targets but are typically synthesized following an iterative approach. Herein, we report a visible light-mediated approach to macrocyclic dimers that allows access to 1- and 2-azetine-containing dimeric lactones. Notably, up to 30-membered macrocycles are formed following this strategy that results in 1-azetine dimers via four consecutive triplet energy transfers, while 2-azetines are formed in a sequence relying on two consecutive triplet energy transfers. Computational investigations provide important insights into the reaction mechanism, suggesting that intermolecular [2+2]-cycloadditions are preferred under non-standard Curtin-Hammett conditions over the corresponding intramolecular reaction.

The unique triplet state reactivity of 2-isoxazolines has recently gained attention for their use as protected imine equivalents in photochemical [2+2]-cycloadditions.1–3 Recent work reported by our laboratory has harnessed this triplet state reactivity for the development of an intramolecular [2+2]-cycloaddition between 2-isoxazolines and aryl- and alkyl-substituted alkynes to afford 1- and 2-azetine products, respectively.2 Subsequently, an intramolecular aza Paternò-Büchi reaction was developed, in which 2-isoxazoline 1 containing an unactivated alkene moiety afforded exclusively monomeric, tricyclic azetidine products 2 in up to 84% yield (Fig. 1A).3 While these works display the synthetic utility of 2-isoxazolines, there is a need for further exploration of this functional group in order to expand the scope of reactions enabled by them.

We hypothesized that by changing the alkene moiety in 1 to an alkyne, 3 would react analogously via an intramolecular [2+2]-cycloaddition to provide monomeric, tricyclic azetidine products 4 and 5 (Fig. 1B). This proposed transformation would furnish complex azetine scaffolds in one step, which is an area that remains underdeveloped due to the challenges generally associated with the synthesis of azetines.4–6 However, to our surprise, 3 is found to exclusively undergo an intramolecular [2+2]-cycloaddition to result in the formation of macrocyclic dimeric lactones 6 and 7 (Fig. 1C).

In recent decades, macrocycles have gained prominence in the field of drug discovery, despite tending to disobey properties that are seen as favorable for drug candidates.7 In comparison to small-molecule drugs, macrocycle drugs can offer advantages of improved binding affinity, selectivity, and oral bioavailability due to their size, structure, and complexity.5–10

Figure 1. A. Intramolecular azapaternò-Büchi reaction of 2-isoxazolines and unactivated alkynes. B. Proposed intramolecular aza Paternò-Büchi reaction of 2-isoxazolines and alkynes. C. Dimerization-macrocyclization of 2-isoxazolines.
However, there remains a dearth of robust synthetic methodology that allows for access to structurally diverse analogs of macrocycles, hence deterring the exploration of this class of compounds in medicinal chemistry.

Specifically, naturally occurring macrocyclic dimeric lactones are a class of macrocycles that has captured the attention of synthetic chemists due to their known biological activity and structural complexity (Fig. 2).\textsuperscript{11-16} However, many reported syntheses construct the macrocyclic core iteratively, closing the macrocycle over multiple esterification or ring-closing metathesis steps.\textsuperscript{12-14,16} In contrast, there are few examples of the monomeric unit of the macrocycle being directly dimerized to the desired natural product.\textsuperscript{11,15}

As such, while direct dimerization approaches do exist,\textsuperscript{17} there remains an unmet need for strategies to access macrocyclic scaffolds via novel approaches. Herein, we report the development of a visible-light-mediated method for the direct dimerization of distal-alkyne-substituted 2-isoxazolines, which provides 1- and 2-azetine-containing dimeric lactones of up to 30-membered ring macrocycles. This transformation provides access to previously inaccessible chemical space, expanding the scope of azetine-containing compounds for potentially biologically interesting applications.

Initial investigations into the development of this visible-light-mediated direct dimerization began with subjecting 2-isoxazoline 10 to conditions previously reported for the intermolecular [2+2]-cycloaddition of 2-isoxazolines and alkenes.\textsuperscript{2} Specifically, conversion of 10 with catalytic amounts of [Ir(dFppy)\textsubscript{2}(dppbpy)]PF\textsubscript{6} (Ir1 PF\textsubscript{6}) upon irradiation with 427 nm light in acetonitrile provided 1-azetine dimer 11 in 64% yield and 1.8:1 d.r. (Table 1, entry 1). Surveying photocatalysts fac-[Ir(dFppy)\textsubscript{3}] and 2CzPN with triplet energies equivalent to that of Ir1 PF\textsubscript{6} resulted in diminished yields for 11 of 37% and 43%, respectively (Table 1, entries 2 and 3). This could be attributed to the oxidation potentials (E\textsubscript{ox}) of fac-[Ir(dFppy)\textsubscript{3}] and 2CzPN, which are lower (E\textsubscript{ox} = -1.28 V and -1.30 V, respectively) than that of Ir1 PF\textsubscript{6} (E\textsubscript{ox} = -0.89 V) and could subsequently lead to decomposition of 11. Interestingly, using photocatalysts with lower triplet energies, such as [Ir(dFppy)\textsubscript{2}(dppbpy)]PF\textsubscript{6} (Ir2 PF\textsubscript{6}), resulted in slightly elevated yields for 11 of 51% and 45%, respectively (Table 1, entries 4 and 5).

We hypothesized that conducting the reaction at lower concentrations could favor the formation of the monomeric tricyclic 1-azetinyl 4 that would arise from an intramolecular [2+2]-cycloaddition of 10. For the analogous intramolecular [2+2]-cycloaddition of 2-isoxazolines 1 and unactivated alkenes, this strategy addressed competing intermolecular reaction pathways and resulted in significantly improved yields for low-yielding substrates.\textsuperscript{3} However, surprisingly, running this reaction at 0.05, 0.01, and 0.0025 M still resulted in exclusive formation of 11, albeit in diminished yields of less than 52% (Table 1, entries 6, 7, and 8).

With the optimal photocatalyst and solvent concentration identified, subsequent efforts focused on exploring the role of solvent in product yield and diastereoselectivity. The reaction was found to proceed in dichloromethane, methanol, and toluene to provide yields for 11 of up to 47% (Table 1, entries 9, 11, and 12). No conversion of 10 was observed in tetrahydrofuran
Figure 3. Evaluation of the scope of 1-azetine dimer formation. Conditions: 0.2 mmol 2-isoxazoline and Ir1·PF6 (1.0 mol%) are dissolved in acetonitrile (0.1 M), and the solution is sparged for 10 min. The reaction is irradiated with blue LED lamps (427 nm) for 16-18 h.

(Table 1, entry 10). Interestingly, toluene provided 11 with the highest diastereomeric ratio of 3.5:1 and 2.6:1 d.r. (Table 1, entries 3 and 12). Ultimately, the optimized conditions were selected as 1 mol % Ir1·PF6 in 0.1 M acetonitrile.

Next, the scope of 1-azetine dimer formation was evaluated (Fig. 3). This reaction was shown to tolerate different aryl substitution patterns, linker substitution, and linker lengths, providing 1-azetine dimers in up to 44% yield. Aryl groups with an electron-withdrawing substituent (12) resulted in 44% yield, proving to be superior to unsubstituted aryl groups (11, 14-20) and aryl groups with an electron-donating substituent (13), the latter of which resulted in 35% yield. Increased steric bulk via substitution of the alkyne-ester linker (14) proved to hinder reactivity and resulted in 6% yield. This is likely due to the Thorpe-Ingold effect, which would favor intramolecular cyclization which, in this reaction, leads to reversion to starting material under non-standard Curtin-Hammett conditions (see mechanistic studies below).

The ability to increase the linker length of the oxime was of particular interest, as this would provide a unique way to construct functionalized macrocyclic dimeric lactones in one step, obviating the need for iterative macrolactonization strategies that are generally employed in the syntheses of such scaffolds.12-14,16 12-, 14-, and 16-membered macrocycles (15-17) were readily accessible in 30%, 21%, and 28% yield, respectively. Furthermore, 18- and 20-membered macrocycles (18, 19) were also accessible, albeit in decreased yields of 17% and 13%, respectively. Notably, we were able to isolate the 30-membered macrocycle 20 in 10% yield, which, while low-yielding, exhibits the power of this method as 20 is the only observed product from the reaction.

Based on previously reported work, in which alkynes bearing alkyl substituents underwent an intermolecular [2+2]-cycloaddition with 2-isoxazolines to afford 2-azetines,2 we sought to investigate the compatibility of alkyl-substituted 2-isoxazolines with the previously optimized reaction conditions. Reaction of the methyl-substituted 2-isoxazoline provided 2-azetine dimer 21 in 41% yield (as determined by 1H NMR with mesitylene internal standard). An increase in yield from 41% to 47% was observed upon increasing the concentration to 0.2 M (35%
Figure 4. Evaluation of the scope of 1-azetine dimer formation. Conditions: 0.2 mmol 2-isoxazoline and \textit{Ir1-PF}\textsubscript{6} (1.0 mol\%) are dissolved in acetonitrile (0.2 M), and the solution is sparged for 10 min. The reaction is irradiated with blue LED lamps (427 nm) for 16-18h.

Figure 5. Mechanistic hypotheses for the formation of 1-azetine (11) and 2-azetine (21) dimers.
isolation of a dimeric lactone (see Supporting Information for more details).

Proceeding with these new conditions, the scope of 2-azetine dimer formation was subsequently investigated (Fig. 4). An ethyl group (22) was found to be comparable to 21, resulting in 36% yield. Adding steric bulk to the alkyne resulted in diminished yields, with isopropyl (23) and tert-butyl groups (24) providing the desired products in 19% and 26% yield, respectively. Cyclic alkyl groups (25-27) were also tolerated in lower yields, resulting in yields of up to 20%. Motivated by previous successes in obtaining up to 30-membered macrocycles for the 1-azetine dimers, the accessibility of larger ring sizes for the 2-azetine dimers was investigated. However, while the formation of the corresponding methyl-substituted 12-, 14-, and 16-membered macrocycles (28) were observed, these products were

Based on previous work for the synthesis of 1- and 2-azetines, the following mechanism for dimerization is proposed (Fig. 5). Upon irradiation with visible light, a photoexcited triplet state iridium photocatalyst sensitizes cyclic oxime 29 by triplet energy transfer. The resulting triplet state oxime 1-I then undergoes an intermolecular [2+2]-cycloaddition with the alkyne moiety of a ground-state molecule of 29 to form intermediate I-2. For I-2 in which R = alkyl, I-2 is only able to undergo a second energy transfer via sensitization of the isoxazoline, resulting in the triplet state intermediate I-3. This subsequently undergoes an intramolecular [2+2]-cycloaddition to form the 2-azetine dimer 21. In contrast, for I-2 in which R =

Figure 6. Rationale for the formation of macrocyclic, dimeric lactones upon excitation of alkynes 3 in comparison to the formation of [2+2]-cycloaddition products (2) from alkenes 1.

non-isolable due to the presence of an inseparable impurity.
aryl, the styrene moiety is preferentially sensitized to provide the triplet biradical intermediate I-4. This results in the rearrangement of I-4 via N-O bond cleavage, intersystem crossing to the corresponding singlet state, and radical recombination to the azetine intermediate I-5. Upon a third triplet energy transfer to the isoxazoline of I-5, cyclization occurs via an intramolecular [2+2]-cycloaddition to generate I-7. A final sensitization of the styrene moiety of I-7 and subsequent rearrangement leads to the desired azetine dimer I1.

Subsequent efforts were focused on conducting mechanistic investigations using density functional theory (DFT) to probe why dimerization of alkenes such as 10 was favored over the initially hypothesized intramolecular [2+2]-cycloaddition. All geometry optimization and frequency calculations were performed using B3LYP functional with D4 dispersion correction using DEF2-SVP basis set. Single point calculations were carried out using oB97x functional with D4 dispersion correction, DEF2-TZVPPD basis set and implicit acetonitrile solvent using CPCM. Following the excitation of the 2-oxazoline, initial C-C bond formation for the intramolecular reaction is kinetically accessible both for alkyne (3, Fig. 1A) and alkene (1) substrates, requiring a barrier of 12.0 and 8.9 kcal/mol (TS11 and TS31), respectively (Fig. 6). C-C bond formation for both alkyne and alkene substrates is reversible and exergonic by 19.6 and 20.1 kcal/mol, respectively. Following the formation of the product and triplet to singlet relaxation trough intersystem crossing, singlet diradical intermediates can undergo either radical recombination reaction to form the corresponding azetine or azetidine products, or C-C bond cleavage to regenerate singlet starting material. The barrier for the reverse reaction to regenerate the starting material for both intermediates is approximately 4–5 kcal/mol. However, the radical recombination barrier for forming the azetine is only 3.0 kcal/mol and is therefore kinetically favored over the reverse reaction on the singlet surface.

On the other hand, the barrier for azetine formation is 10.2 kcal/mol. The difference in reactivity can be attributed to a significant distortion of the bridging sp² carbon (Fig. 6), where the highlighted CCC angle in TS2 is has a significantly higher strain (137.7°) when compared to the transition state of the alkene analog (TS4, 116.9°). This observation

Figure 7. Computational investigations of aliphatic alkenes in the visible light-mediated [2+2]-cycloaddition resulting in dimeric, macrorcyclic lactones.
Figure 8. Spin density analysis of triplet-optimized states for aliphatic and aryl alkynes.

Figure 9. Computational investigations of aromatic alkynes in the visible light-mediated [2+2]-cycloaddition resulting in dimeric, macrocyclic lactones.
was further confirmed by performing an intramolecular activation strain model (see Supplemental Information for details), which revealed that both alkyne and linker strain increased by approximately 5 kcal/mol relative to the alkene transition state (Fig. 6). Therefore, despite a relatively low barrier for the initial C-C bond formation, the formation of the intramolecular [2+2] addition product is not accessible due to the reversibility of the C-C bond adduct on the singlet surface and increased barrier of radical recombination reaction arising from rigid bridging sp² carbon center.

Instead, the alkyne moiety can undergo an intermolecular dimerization reaction (Fig. 7). The barrier for the initial C-C bond formation (TS₅) requires activation energy of 16.3 kcal/mol, which is higher than the barrier for the C-C bond formation of intramolecular reaction (12.0 kcal/mol, TS₁³). However, due to the reversibility of the intramolecular intermediate on the singlet surface, the reaction is under non-standard Curtin-Hammett conditions, where kinetically less favorable, but the irreversible pathway becomes the predominant product. The higher barrier for the intermolecular reaction can be primarily attributed to the loss of the translational entropy of the bimolecular reaction.

Following the formation of the C-C bond adduct VII (ΔG = −9.5 kcal/mol), and intersystem crossing to the singlet intermediate, the radical recombination reaction proceeds through a near barrierless transition state (TS₆³), whereas the singlet C-C dissociation to regenerate the starting material requires activation energy of 8.9 kcal/mol (TS₇³). Following the formation of the first [2+2]-cycloaddition adduct, another excitation of the 2-isoxazoline can occur, which undergoes C-C bond addition with a barrier of 10.0 kcal/mol (TS₇³). After the formation of the triplet adduct, another intersystem crossing and radical recombination reaction takes place, which leads to the formation of the final dimerization product.

To understand the origin of reactivity differences between alkyl- and aryl-substituted alkynes, we performed time-dependent DFT calculations to analyze triplet excited states of [2+2]-cycloaddition intermediates. Both transition energies and density difference plots indicate distinct behavior of these two compounds. Energetically, excitation of alkylated intermediate to the T1 state is more favorable, and density difference analysis indicated that the excitation involves styrene moiety, while the T2 state corresponds to the activated 2-isoxazoline. Because the alkylated substrate does not lead to the formation of activated alkyne, 2-isoxazoline moiety is excited in the T1 state, and the excitation of alkene (T2 state) has significantly higher transition energy. The identity of triplet-optimized states for these two intermediates was also confirmed using spin density analysis (Fig. 8).

Based on this understanding, we analyzed the reaction mechanism for arylated substrates (Fig. 9). In this reaction, the initial intramolecular C-C bond formation (TS₈) requires a barrier of 12.1 kcal/mol. Following the intersystem crossing, the radical recombination reaction has a barrier of 4.4 kcal/mol, which leads to the formation of [2+2]-cycloadduct. Following the excitation of the intermediate XIV, N-O cleavage proceeds with a lower barrier of 6.7 kcal/mol, and the reaction is exergonic by approximately 25 kcal/mol. Following the intersystem crossing and radical recombination, rearranged intermediate is formed. Two additional excitations (Fig. 9) lead to a second [2+2]-cycloaddition with a barrier of 9.6 kcal/mol for C-C bond formation (TS₁₁³), and rearrangement with a barrier of 7.6 kcal/mol for N-O cleavage transition state (TS₁₃³).

In conclusion, we report the development of a visible-light-mediated direct dimerization of distal-alkyne-substituted oximes. This unexpected intermolecular [2+2]-cycloaddition outcompetes the initially hypothesized intramolecular reaction pathway under non-standard Curtin-Hammett conditions, allowing for access to 1- and 2-azetine-containing macrocyclic dimeric lactones of up to 30-membered rings. Notably, this transformation occurs in one step and deviates from traditional macrocyclization methods. We anticipate that this new method will provide a unique avenue to accessing biologically interesting macrocycles.

ASSOCIATED CONTENT
Supporting Information. This material is available free of charge – Experimental procedures, characterization (¹H NMR, ¹³C NMR, IR, and MS data), additional optimization, and control experiments.

Accession Codes. CCDC 2211280 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION
Corresponding Authors
Heather J. Kulik – Massachusetts Institute of Technology, Department of Chemical Engineering, Cambridge, MA 02139, United States; Email: hjkulik@mit.edu
Corinna S. Schindler – University of Michigan, Department of Chemistry, Willard Henry Dow Laboratory, Ann Arbor, Michigan 48109, United States; Email: corinnas@umich.edu

Authors
Scott L. Kim – University of Michigan, Department of Chemistry, Willard Henry Dow Laboratory, Ann Arbor, Michigan 48109, United States
Scott L. Kim – University of Michigan, Department of Chemistry, Willard Henry Dow Laboratory, Ann Arbor, Michigan 48109, United States
Ilia Kevlishvili – Massachusetts Institute of Technology, Department of Chemical Engineering, Cambridge, MA 02139, United States; Email: hjkulik@mit.edu

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Notes
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REFERENCES


