Iridium Acylnitrenoid-Initiated Biomimetic Cascade Cyclizations: Stereodefined Access to Polycyclic δ-Lactams

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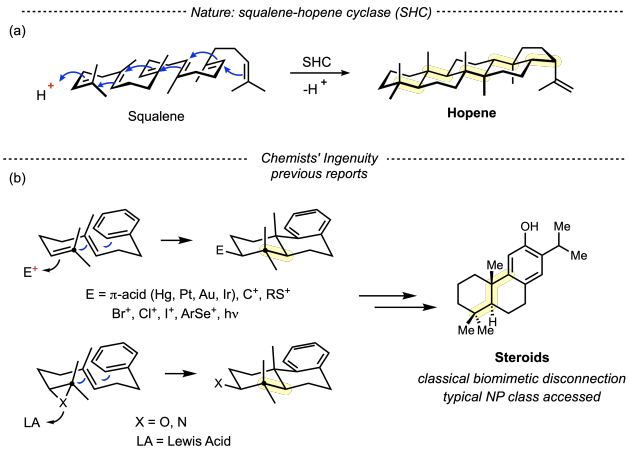
ABSTRACT: Ring-fused azacyclic compounds are an important building unit in the synthesis of biorelevant natural products, pharmaceutical agents, and molecular materials. Herein, we present a new approach to these condensed azacycles by a biomimetic cascade cyclization of arylalkenyl dioxazolones. This cascade reaction was found to proceed with excellent stereoselectivity and high functional group tolerance. The substrate scope of arylalkenyl dioxazolones was turned out to be highly flexible and extendable to additional terminating subunits such as heteroaryl and alkynyl moieties. This biomimetic cyclization was elucidated to initiate by an intramolecular transfer of the *in situ* generated electrophilic Ir-acylnitrenoid species to the olefinic double bond. This leads to a key *N*-acylaziridine intermediate which is in turn, reacted with pendant (hetero)arenes or alkynes in highly regio- and stereoselective manner to produce ring-fused azacyclic compounds.

INTRODUCTION

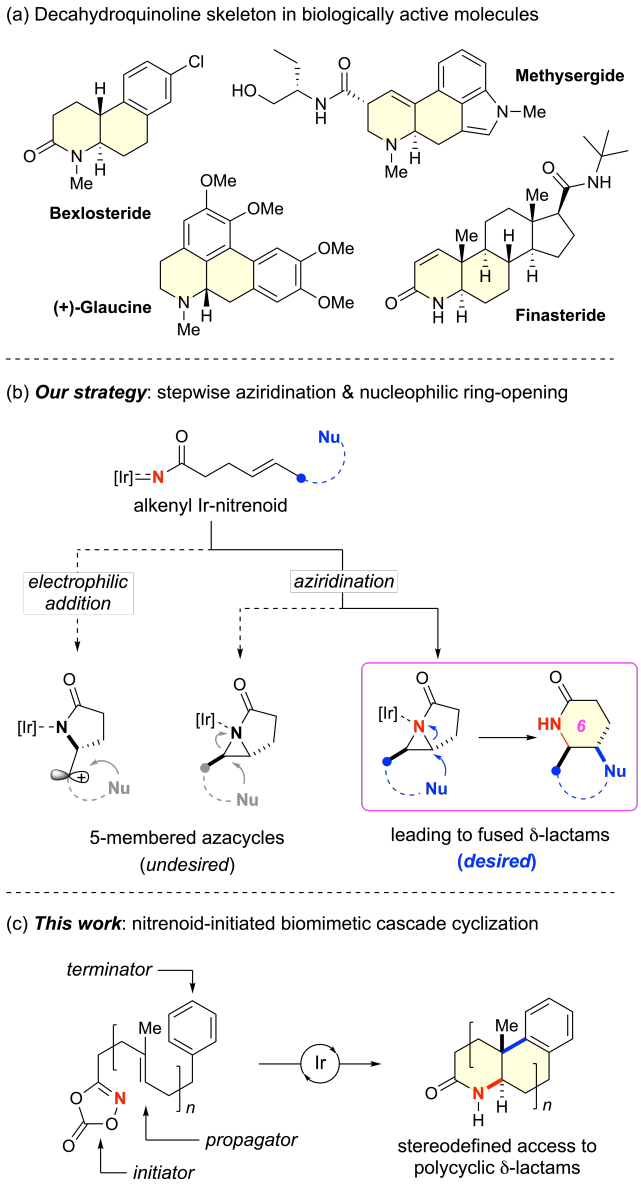
Biomimetic cyclizations serve as one of Nature's most powerful and marvelous synthetic tools, well exemplified by squalene hopene cyclase being responsible for catalyzing the enantioselective cyclization of squalene (Scheme 1a). In this process, an initiation via protonation of the terminal isoprene functionality ends up forming nine stereocenters of five new carbon−carbon bonds and five carbocycles, all in a single synthetic step.[1] A remarkable level of selectivity can be achieved via this cyclization, especially considering the fact that thousands of isomers would be theoretically generated via alternative chemo-, regio-, and stereoselective pathways. Notably, the stereochemistry of the entire process is highly predictable based on the Stork–Eschenmoser postulate,[2] wherein the carbocation propagation is governed by the defined polyolefin conformations, e.g. via either chair- or boat-like transition states in the cyclohexane ring formation with antiperiplanar addition to the double bonds. Due to the central role played by the carbocation, these cyclizations are collectively referred as the cationic polyene cyclizations, also known as cation π-cyclizations,[3] which unravel their synthetic efficiency by virtue of a concerted and asynchronous route generating a carbocationic intermediate. Concerted "propagation" of carbocations[4] on a polyolefin chain forges carbocyclic rings and, thereafter, a terminating-event quenches the corresponding carbocation. On the other hand, chemists have devised a number of interesting biomimetic variants of the cascade cyclization process over the years, especially to focus on the initiating groups, olefin geometry, (chiral) reagents and catalyst systems; all contributing to the repertoire of the available approaches, thereby eventually allowing for highly productive multiple cyclizations (Scheme 1b).[5] In addition to the traditional biomimetic polar cyclization process, the radical pathway has also been explored to access analogous ring-fused frameworks.[6]

Scheme 1. Cascade Cyclization Approaches



However, it should be mentioned that, despite the notable achievements relying on biomimetic cyclizations, most of them begin with the formation of a discrete or formal carbocation intermediate. The consecutive Markovnikov-type addition to the π-system forges a new carbon-carbon bond with the formation of carbocyclic rings. Surprisingly, initiation sites containing atoms other than carbon have been underexplored. As a consequence, polyene cyclizations performed by synthetic chemists, as well as Nature, are mainly limited to the synthesis of carbocyclic cores at the present stage.

Scheme 2. Ir-acylnitrenoid-initiated Cascade Polycyclization.



Realizing this limitation and lack of utility for ring-fused *heterocyclic* compounds, we envisioned that engineering a cascade cyclization process, in which a heteroatom may be introduced into the core skeleton of cyclic products, would provide a new opportunity to delve into chemically more diverse heterocyclic structures. In particular, we were motivated by the fact that ring-fused azacycles are an important building block for the synthesis of natural products, pharmaceutical agents and molecular materials (Scheme 2a).[8]

Among them, terpenoid alkaloids and aza-steroids are a captivating class of such biorelevant ring-fused azacycles. Indeed, the former is an intriguing skeleton of natural compounds that arise from the incorporation of a nitrogen atom during the biosynthetic process mediated by cyclases.[9] Characterized by their interesting biological properties, some of these compounds are still elusive from the synthetic perspective and, therefore, new methodologies are highly desirable, especially those that could assemble the heterocycle rings by exploiting the rapid stereoselective forging performance peculiar to the biomimetic cyclization reactions. Aza-steroid are structurally modified steroids which are endowed with a wide range of pharmacological activities,[10] representatively Finasteride, the first clinically used inhibitor of Type II steroid 5α-reductase used for the treatment of benign prostatic hyperplasia and an oral drug for male pattern hair loss.[10b, 11]

While the exploitation of biomimetic cyclizations to form both oxygen and nitrogen heterocycles has been achieved, the design situates the heteroatom as a linchpin between the initiator and terminator group or it represents trapping of the nucleophilic terminating groups.[5f,7] With these considerations in mind, we hypothesized that a cyclization cascade initiated by a nitrenoid transfer would enable access to the aforementioned condensed δ-lactam compounds (Scheme 2b). We envisaged that, among various approaches to reverse the polarity of the transferring amino groups,[12] electrophilic metal nitrenoid reactivity would be an attractive strategy,[13] thus forming a bicyclic aziridine intermediate that can subsequently be reacted with a tethered nucleophile in an intramolecular manner to give rise to condensed azacyclic products. In this approach, in addition to the efficiency of the initial aziridination step, there is another critical issue on the subsequent intramolecular ring-opening with nucleophiles to determine the ring size of condensed azacyclic products (5- vs 6-membered lactams). We also wondered whether our cyclization approach could be further extended to a cascade procedure.

Herein we present a biomimetic cascade cyclization of arylalkenyl dioxazolones to furnish condensed azacyclic compounds with excellent stereoselectivity (Scheme 2c). Substrate scope was explored to find that terminating subunits would be highly flexible to accommodate heteroaryl and alkynyl moieties in addition to arenes. This cascade cyclization was elucidated to proceed with an initial intramolecular transfer of electrophilic Ir-acylnitrenoid to the neighboring double bond leading to key bicyclic *N*-acylaziridine intermediate, which is subsequently reacted with pendant terminating nucleophiles to produce ring-fused δ-lactam compounds in a highly regio- and stereoselective manner. It should be noted that neither existing hydroamination methods,[14] including a hydroboration-based approach developed by Shenvi,[15] cannot be applied for the polyene biomimetic cyclizations as the required propagation event for the cascade cyclization is precluded.

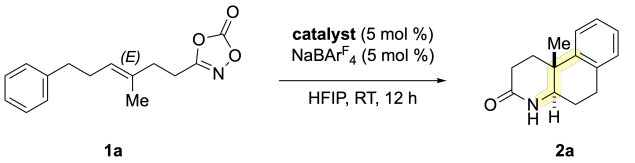
RESULTS AND DISCUSSION

To validate our working hypothesis, (*E*)-phenylalkenyl dioxazolone **1a** was designed to examine if a biomimetic cyclization would indeed be triggered by the *in situ* generation of an electrophilic nitrene (Table 1). Noteworthy the dioxazolones utilized in this study can be readily prepared in two steps from the corresponding carboxylic acid precursors with high overall yields.[16] We observed that the desired cyclization of **1a** took place when Cp*Ir(III) catalyst (**Ir1**, 5 mol %) bearing 8-hydroxyquinoline ligand was employed in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent at room temperature for 12 h (entry 1), conditions which were proved to effectively catalyze C-H amidation in previous reports.[16c-e] The reaction furnished tricyclic δ-lactam product **2a** (17%) and isocyanate derivatives (<5 %). The structure of tricyclic lactam **2a** was unambiguously confirmed by an X-ray crystallographic analysis (*vide infra*), revealing the *trans*-fused decahydroquinolinone skeleton. It needs to be emphasized that the present reaction would be considered as a biomimetic cascade cyclization in that three-ring assembly is achieved in one-operation in a perfectly stereoselective manner.[1, 17]

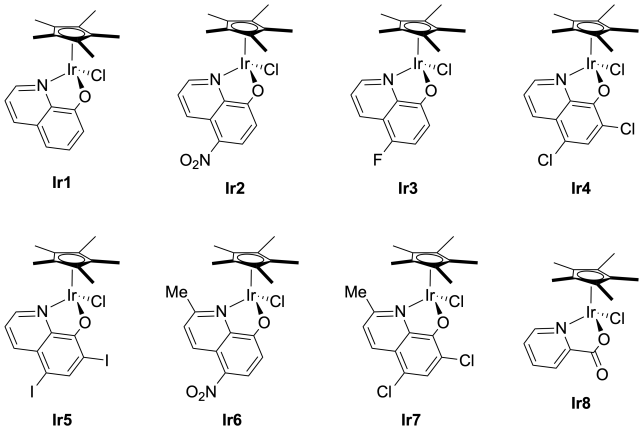
It was found that variation of the LX-type co-ligand in the Cp*Ir(III)(κ^2-LX) catalyst system notably influences the reaction efficiency while the perfect *trans*-diastereoselectivity was maintained in all cases examined. For instance, catalyst **Ir2** bearing a 5-nitro substituent in the 8-hydroxyquinoline skeleton increased the product yield (44%) with high conversion under otherwise identical conditions (entry 2). However, installation of halides such as fluoro (**Ir3**), chloro (**Ir4**), or iodo (**Ir5**) groups at the hydroxyphenyl moiety was found to be less effective when compared to the nitro substituent (entries 3–5). In stark contrast, the introduction of a methyl group at the C2-position of 8-hydroxyquinoline co-ligand resulted in significantly improved cyclization efficiency. For instance, catalyst **Ir6** bearing 2-methyl-5-nitro-8-hydroxyquinoline promoted the current reaction to 65% yield (compare entries 2 and 6). Moreover, the best catalytic performance was observed with catalyst **Ir7** which was derivatized to have two chloro substituents along with one methyl group in the κ^2-LX co-ligand (entry 7). An iridium catalyst **Ir8** derived from picolinic acid displayed only low cyclization efficiency to give rise to 2a in 11% yield (entry 8). It should be mentioned that the current cyclization is catalytic in the iridium complexes employed in that no reaction took place in the absence of such catalyst (entry 9).

With the optimal catalytic protocol in hand, we next evaluated the generality of our newly developed cascade cyclization on (*E*)-configurated substrates **1a-g** bearing several aryl terminating groups (Chart 1). A broad range of arenes including substituted-phenyl (**1a-1d)** and naphthyl (**1e**) moieties proved to be efficient nucleophilic terminators for this nitrenoid-initiated biomimetic cyclization. In general, cyclization products were formed in synthetically useful yields and, importantly, as a single diastereoisomer, affording the *trans*-fused decahydroquinolinones system exclusively. All reactions were conducted at ambient temperature under air with commercial-grade solvents and reagents, thus making this cyclization protocol highly convenient to perform. Moreover, this process could be scaled up to 2 mmol of **1b** with 91% isolated yield of the corresponding product **2b**.

Table 1. Optimization of Ir Catalysts Toward Cascade Cyclization[a]

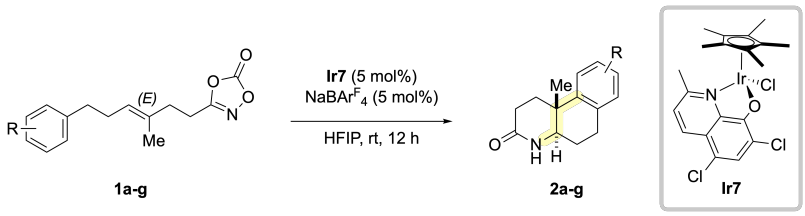


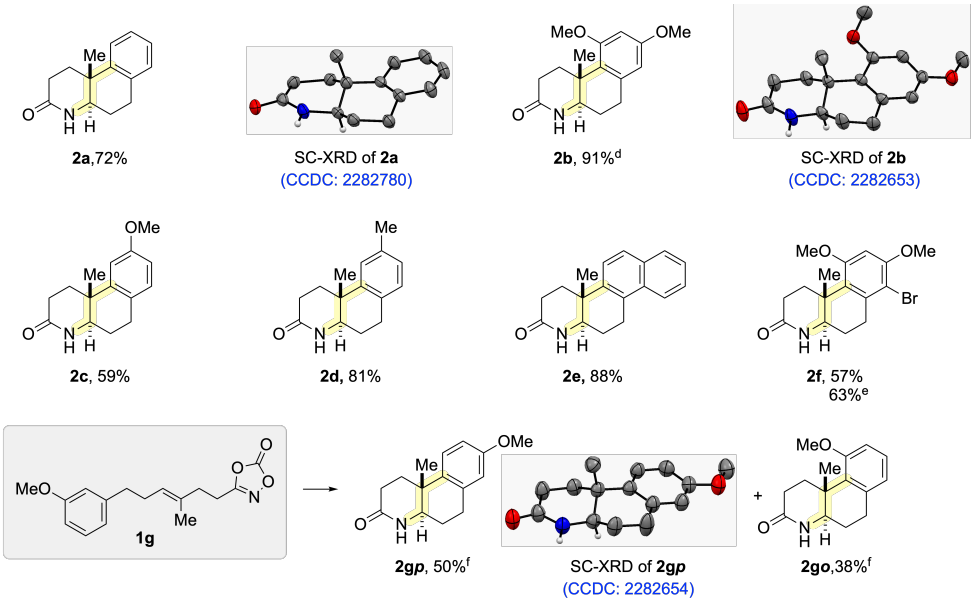
entry	catalyst	conversion (%)	yield (%)
1	**Ir1**	22	17
2	**Ir2**	77	44
3	**Ir3**	73	10
4	**Ir4**	24	16
5	**Ir5**	57	27
6	**Ir6**	>95	65
7	**Ir7**	>95	72
8	**Ir8**	11	11
9	none	< 5	N.D.
10	**Ir7**	80	68[b]
11	**Ir7**	13	7[c]

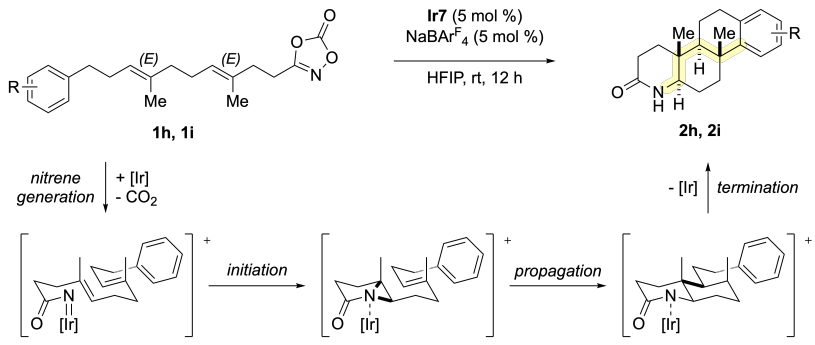


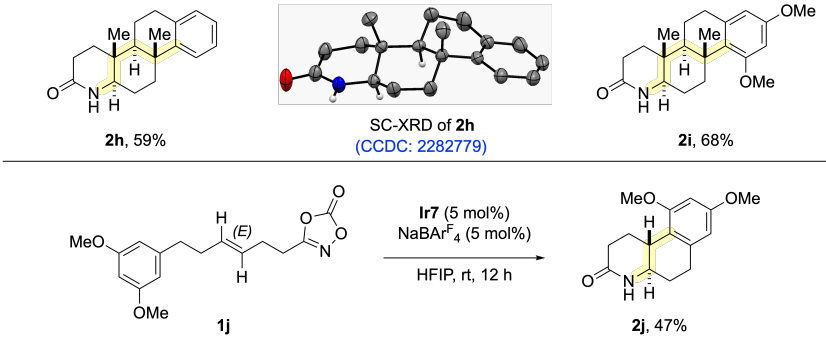
[a]Conditions: **1a** (0.1 mmol), catalyst (5 mol %) and $NaBArF_4$ (5 mol %) in HFIP (0.5 mL) at room temperature for 12 h: yields were determined by 1H NMR spectroscopy using dibromomethane (0.1 mmol) as an internal standard. [b]Nonafluoro-*tert*-butyl alcohol (NFTB) was used as the solvent instead of HFIP. [c]Dichloromethane was used as the solvent instead of HFIP.

Chart 1. Cyclization Scope of (*E*)-olefinic Dioxazolone Substrates[a,b,c]









[a]Conditions: substrate **1** (0.1 mmol, 1.0 equiv.), **Ir7** (5 mol %), NaBAr$^F_4$ (5 mol %), and HFIP (0.2 M) at room temperature for 12 h. [b]Isolated yields. [c]The relative *trans* configuration of **2** was determined using NMR spectroscopy and single crystal X-ray diffraction (SC-XRD) analysis. [d]Run on 2 mmol scale. [e]Yield from one-pot procedure (*vide infra*). [f]88% Combined yield of a separable (1.3:1) mixture of *para*- (**2g*p***) and *ortho*-regioisomer (**2g*o***), respectively.

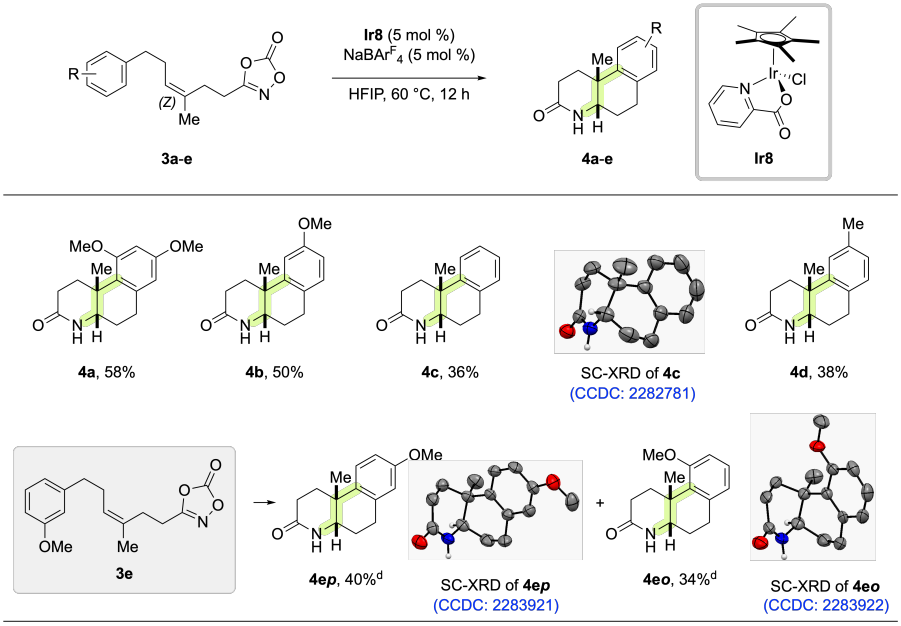
Interestingly, a substrate bearing densely substituted bromophenol ring was viable for the current cascade cyclization to afford decahydroquinolinone **2f** in 57% yield, which may offer an opportunity for further functionalizations, *e.g.* cross-coupling reaction. Notably, product **2f** could be prepared in a one-pot procedure starting from substrate **1b**, wherein exposing **1b** to NBS in HFIP at 20 °C afforded the substrate **1f**. Then, without isolation, a simple addition of **Ir7** (5 mol %) and $NaBAr^F_4$ (5 mol %) afforded the desired decahydroquinolinone **2f** in 67% yield. This example clearly demonstrates the robustness of our Ir-mediated electrophilic nitrene cyclization. When *meta*-MeO-substituted phenyl substrate **1g** was employed, terminating cyclization took place both at the *para*-position (**2gp**, relative to methoxy group) and at the *ortho*-position (**2go**) almost non-selectively (**2gp/2go**, 1.3:1), both of regioisomers were readily separated by silica gel column chromatography. However, the reaction of substrates bearing a chloro or a trifluoromethyl substituent in the *para*-position on the aromatic ring were not successful, even with elevated temperature and higher catalyst loading. A possible reason can be found in the electron withdrawing properties of the substituents, which decreases the electron density on the aromatic core and thus disfavor the cyclization step.

The above successful dicyclization of arylalkenyl dioxazolones furnishing tricyclic lactam products led us to examine the capability of this cyclization protocol toward tricyclization of bisolefinic substrates. We anticipated that this cascade event would also be initiated by an iridium acylnitrenoid transfer to the neighboring olefin to afford an aziridine intermediate which will be further reacted with the remote olefin and then finally with tethered phenyl in sequence. To our delight, this class of (*E,E*)-diolefinic phenyl dioxazolones **1h–i** were found to readily undergo the desired tricyclization by the action of **Ir7** catalyst in HFIP solvent to provide tetracyclic products (**2h**-**2i**) in satisfactory yields. Remarkably, only one diastereomer bearing four new consecutive stereogenic carbon centers was produced in each case.

With the aim to also test alternative alkene substitution patterns, we prepared the substrate **1j** without the methyl substituent. The reaction occurred by affording the desired product **2j** with 47% isolated yield, thus supporting the robustness of our method.

Based on the result obtained from the *trans*-selective cyclization of (*E*)-olefinic dioxazolone substrates, we wondered whether corresponding (*Z*)-olefin stereoisomeric counterparts could also be cyclized to afford isomeric products in a stereoselective manner (Chart 2). We were delighted to observe that indeed *cis*-decahydroquinolinone **4a** was obtained exclusively, albeit in low yield (25%, see the supporting information for details) when substrate **3a** was subjected to the standard conditions with **Ir7** catalyst at 60 °C. Significantly, switching the iridium catalyst to the picolinic acid-derived **Ir8** gave rise to product **4a** in improved yield (58%) at 60°C (12 h). Noteworthy is that thermodynamically less stable *cis*-fused decahydroquinolinones[18] were obtained as a single diastereoisomer from (*Z*)-olefinic dioxazolone substrates, thus demonstrating that the cyclization proceeds highly stereoselectively.

Chart 2. Cyclization Scope of (*Z*)-olefinic Dioxazolones[a,b,c]



[a]Conditions: substrate **3** (0.1 mmol, 1.0 equiv.), **Ir8** (5 mol %), $NaBAr^F_4$ (5 mol %), and HFIP (0.2 M) at 60 °C for 12 h. [b]Isolated yields. [c]The relative *cis* configuration of the decahydroquinolinone **4** was determined using NMR spectroscopy and single crystal X-ray diffraction (SC-XRD) analysis. [d]74% Combined yield of a separable (1.2:1) mixture of *para*- (**4e*p***) and *ortho*-regioisomer (**4e*o***) respectively.

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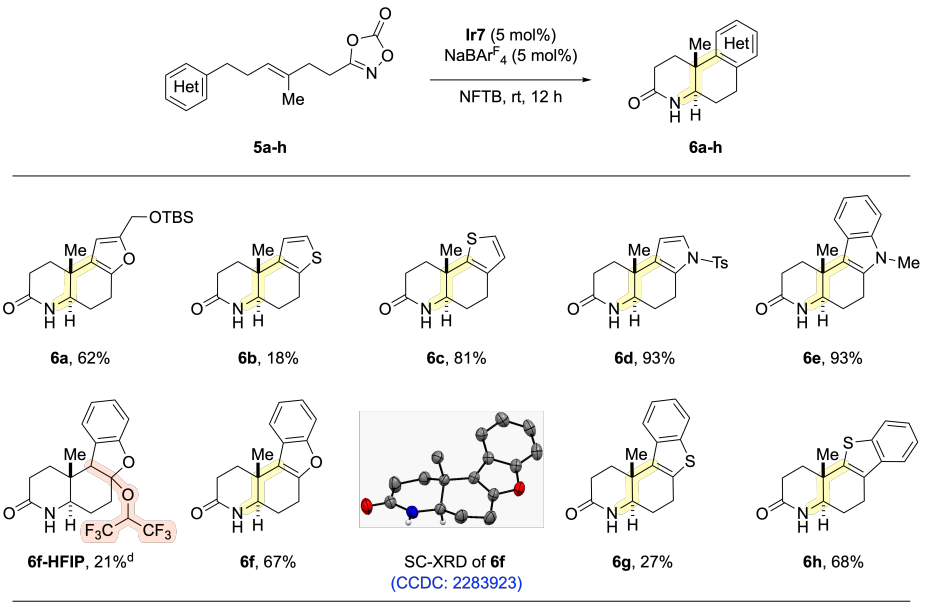
This cyclization scope of (*Z*)-olefinic aryldioxazolones shown, along with their *E*-isomeric reaction outcomes reported in Chart 2, illustrates that each of these electrophilic nitrenoid-initiated cyclizations proceeds through a tight chair-like transition state (Stork-Eschenmoser like hypothesis[19]), where initial alkene geometry is well reflected in the relative stereochemistry of the products. When *meta*-MeO-substituted phenyl substrate **3e** was subjected, terminating cyclization took place at both *para*- (**4ep**) and *ortho*-position (**4eo**), almost non-selectively. It should be mentioned that examples of polyene cyclizations involving (*Z*)-alkene geometry to prepare *cis*-fused decalin systems are in fact quite rare.[20]

Heterocycles also proved to be an effective nucleophilic terminator toward the current cascade cyclization when it is initiated by the iridium acylnitrenoid transfer to the olefinic double bond (Chart 3). In this reaction, switching solvent from HFIP to less nucleophilic NFTB (nonafluoro-*tert*-butanol) turned out to be beneficial in order to prevent the incorporation of HFIP into the polycyclic product skeleton (*e.g.*, compound **6f-HFIP**).[21]

Chart 3. Scope of Substrates with Heterocyclic Terminating Nucleophile[a,b,c]

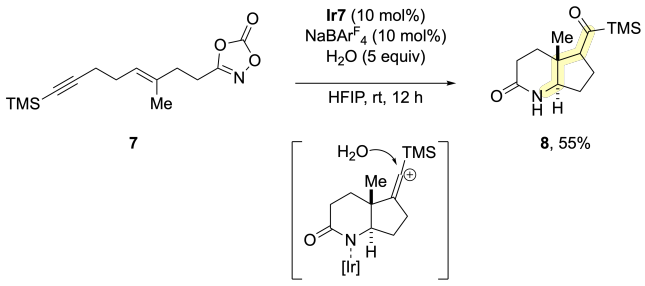


[a]Conditions: substrate **5** (0.1 mmol, 1.0 equiv.), **Ir7** (5 mol %), NaBAr$^F_4$ (5 mol %) and NFTB (0.2 M) at room temperature for 12 h. [b]Isolated yields. [c]The relative *trans*-configuration of the decahydroquinolinone **6** was determined by using NMR spectroscopy and single crystal X-ray diffraction (SC-XRD) analysis. [d]HFIP was used instead of NFTB.

It was observed that olefinic dioxazolones with electron-rich heteroarenes underwent the cascade cyclization to afford the corresponding heterocycle-fused decahydroquinolinones in good to excellent yields. Indeed, a broad range of heteroarenes including furan, thiophene, pyrrole, indole, benzothiophene, and benzofuran were all viable, thus greatly expanding the scope of the current cascade cyclization protocol. Substrates **5b** and **5c** were readily reacted by the action of **Ir7** catalyst to the corresponding cyclized products although the latter was obtained in low yield presumably due to the innate regiochemical preference for the 2 position in the heteroaromatic electrophilic substitution.[22]

Considering the reactivity pattern that C≡C triple bonds located at the 5,6-position relative to a developing cationic center are known to display high tendency to cyclize,[23] feasibility of an alkyne moiety to participate in the present cyclization process was anticipated to be highly intriguing. We were pleased to observe that cyclization of 4,8-enynyldioxazolone substrate **7** was also viable toward cascade ring-closure in the presence of water additive (5 equiv.), presumably serving as an external nucleophile to capture the postulated vinyl cation intermediate (*vide infra*) to furnish the corresponding bicyclic product **8** in 55% yield (Scheme 3).

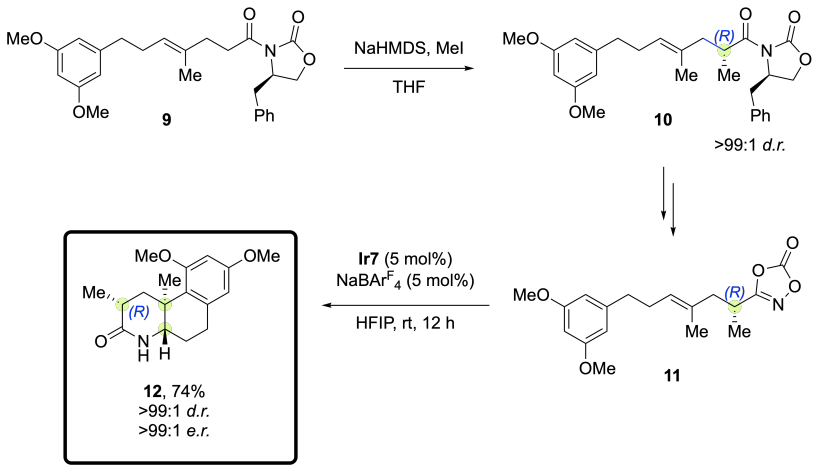
Scheme 3. Cyclization of Alkyne Substrate[a,b,c]



[a]Conditions: substrate **7** (0.1 mmol, 1.0 equiv.), **Ir7** (10 mol %), NaBAr$^F_4$ (10 mol %), HFIP (0.2 M), and 5 equiv. of water additive at room temperature for 12 h. [b]Isolated yields. [c]The relative configuration of the acyl-silane derivative was determined using NMR spectroscopy - NOESY analysis.

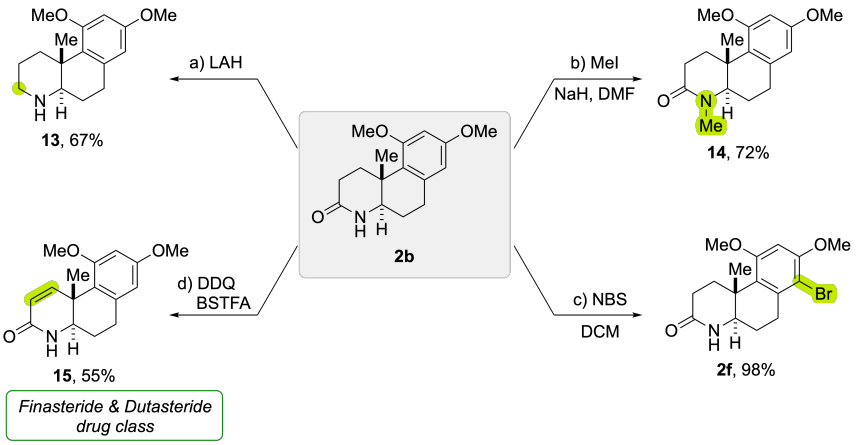
In addition, we briefly investigated the feasibility of extending the present procedure to an enantioselective cyclization (Scheme 4). The required chiral substrate (**11**) was prepared as a single enantiomer (see the Supporting Information for details) by utilizing the Evans-auxiliary procedure from the corresponding chiral amide **10** (single diastereoisomer, ^{1}H-NMR).[24] When optically active α-methyl-dioxazolone **11** (>99:1 *e.r*) was subjected to the standard reaction conditions with **Ir7** catalyst, the desired decahydroquinolinone **12** was isolated in good yield (74%) with excellent diastereo- (>99:1 *d.r.*) and enantioselectivity (>99 *e.r.*).[25] It needs to be emphasized that two stereogenic carbon centers – including one quaternary stereocenter - are newly generated through this diastereoselective cyclization process, suggesting highly ordered transition states.

Scheme 4. Diastereoselective Cyclization of An Optically Active Substrate[a,b,c,d]



[a]Conditions: substrate **11** (0.1 mmol, 1.0 equiv.), **Ir7** (5 mol %), NaBAr$^F_4$ (5 mol %), and HFIP (0.2 M) at room temperature for 12 h. [b]Isolated yields. [c] Enantiomeric and diastereomeric ratio were determined by HPLC on the chiral stationary phase IC-3 column. [d]The relative configuration of the methyl-decahydroquinolinone **12** was determined by using NMR spectroscopy.

Scheme 5. Synthetic Utility of Decahydroquinolinone[a,b]



[a]Conditions: (a) LAH (2 equiv.) in THF (0.2 M) at 50 °C; (b) MeI (2 equiv.) and NaH (2 equiv.) in DMF (0.2 M) at 0 °C to room temperature; (c) NBS (1 equiv.) in dichloromethane (0.2 M) at 0 °C to room temperature; (d) DDQ (1.5 equiv.) and BSTFA (5 equiv.) in 1,4-dioxane (0.05 M) at 100 °C. [b]Isolated yields.

In order to briefly explore the synthetic utility of our present cascade cyclization, substrated decahydroquinolinone **2b** was further transformed as shown in Scheme 5. Amide reduction of tricyclic lactam **2b** was facile with $LiAlH_4$ in THF to afford decahydroquinoline **13** in 67% yield. *N*-methyl derivative **14** was readily obtained from **2b** (72%), and desaturation of **2b** was successfully achieved under DDQ/BSTFA oxidation conditions to furnish **15**, which would be a linchpin for various

inhibitors of type 1 and 2 isoforms of steroid 5α-reductase.[26] Finally, electrophilic aryl bromination of **2b** was carried out highly efficiently to afford **2f** (98% yield), which may serve as a precursor for the subsequent cross-coupling reactions.

We next conducted density functional theory (DFT) computational studies to elucidate the mechanistic pathways of the reaction (Figure 1). The optimal catalyst **Ir7**, and (*E*)-substrate **1b** were utilized to probe the reaction trajectory of the proposed iridium-nitrenoid mediated cascade cyclization. After the coordination of dioxazolone **1b** to the cationic iridium species, the crucial Ir-acylnitrenoid intermediate **I** is generated via the decarboxylation step with a 10.4 kcal/mol barrier (See the Supporting Information for the detailed results).[27] The resulting iridium-nitrenoid intermediate exhibited a π–π interaction between the ligand and the pendant aryl group of the substrate.[28] The distance between the centroids of the aromatic rings is 3.49 Å, which is within the expected distance of a π–π interaction.[29] Based on the premise that iridium-acylnitrenoid intermediates display an electrophilic character,[30] the internal olefin can act as the nucleophile to form the proposed aziridine intermediate **II**. As anticipated, the azabicyclo[3.1.0] intermediate **II** is furnished by traversing **I-TS** with a low barrier of 7.3 kcal/mol relative to **I**, and this process is highly exergonic (ΔG = −23.1 kcal/mol). During this electrophilic nitrenoid addition to the olefin, a significant decrement in the distances between N1 and C5, as well as between N1 and C6, was observed, transitioning from 3.68 Å and 4.41 Å in **I** to 2.21 Å and 2.60 Å in **I-TS**, respectively. Then, the terminating aryl group can undergo conformational rearrangement to **II'**, which features a productive rearrangement for further cyclizations. Here, the aziridination step can be described as an irreversible process that stereoselectively produces the strained aziridine intermediate **II**.[31]

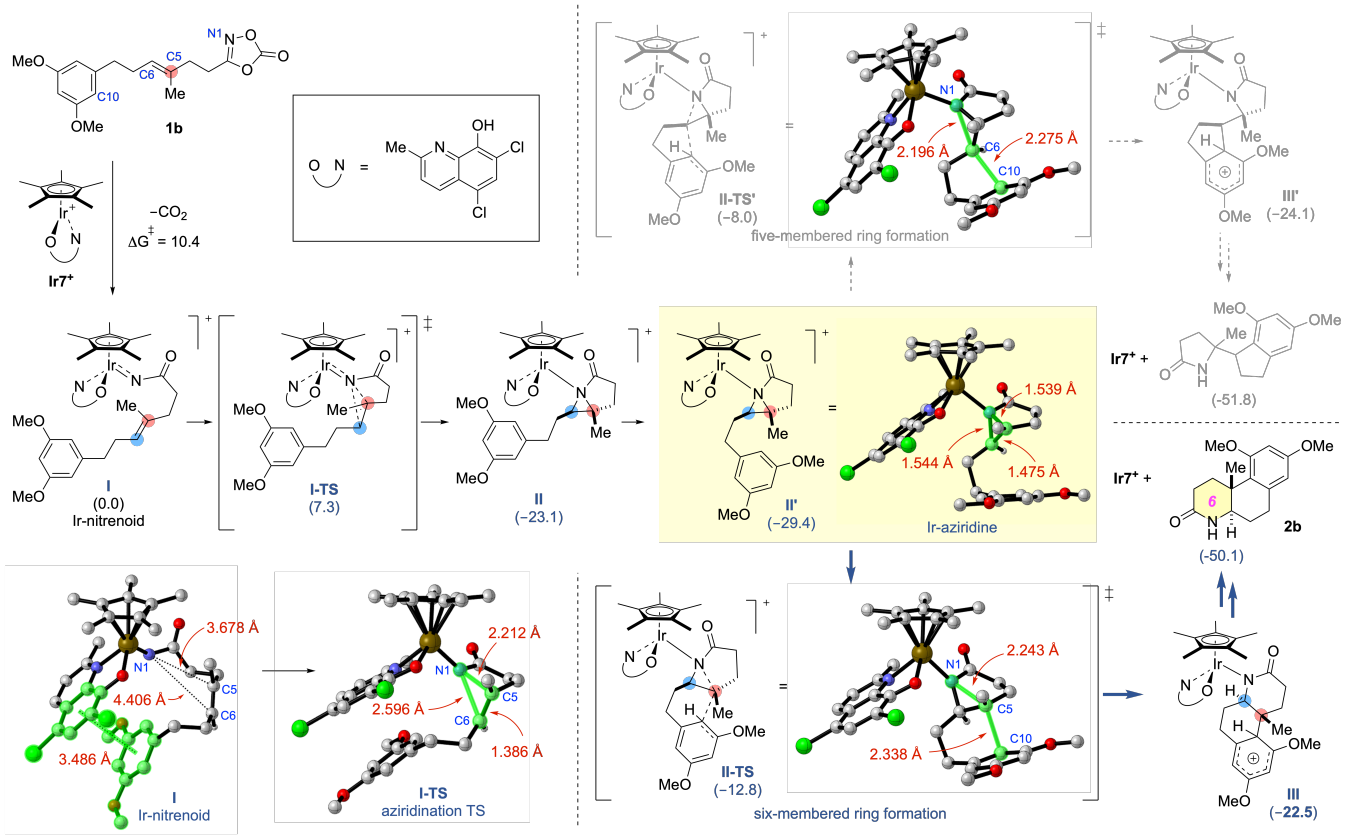


Figure 1. DFT Computational study on Ir-nitrenoid mediated cascade cyclization. Computational level: SMD(HFIP)-B3LYP-D3/6-311+G**|SDD(Ir)//B3LYP-D3/6-31G**|LANL2DZ(Ir).

From the aziridine intermediate **II'**, the pendant aromatic ring can serve as the nucleophile to lead to the formation of either the polyfused δ-lactam (**2b**) or its γ-lactam analog. As the nucleophilic carbon C10 of the aryl ring approaches C5 of the Ir-aziridine complex **II'**, a Wheland intermediate **III** is generated through a six-membered ring transition state **II-TS** with a barrier of 16.6 kcal/mol.[32] A key feature of **II-TS** is the decrease in distance between C10 and C5 (from 2.34 Å to 1.65 Å in **III**), concomitant with an elongation of the N1–C5 bond (from 2.24 Å to 2.48 Å in **III**). The alternative pathway to form the corresponding five-membered analog (**III'**) required a higher barrier by $\Delta\Delta G^{\ddagger}$ of 4.8 kcal/mol via **II-TS'**. Again, this aziridine ring opening proceeds with high stereoselectivity, as it follows a concerted S_N2-like pathway. Further

rearomatization of the Wheland intermediate **III** leads to the formation of polyfused δ-lactam product **2b** along with the cationic iridium catalytic species. Notably, the iridium catalyst may play a key role as the Lewis acid to activate the aziridine moiety, as computations indicate that the analogous metal-free organic aziridine ring opening process shows a higher barrier ($\Delta G^{\ddagger}$ = 28.9 kcal/mol, see the Supporting Information for the detailed results).

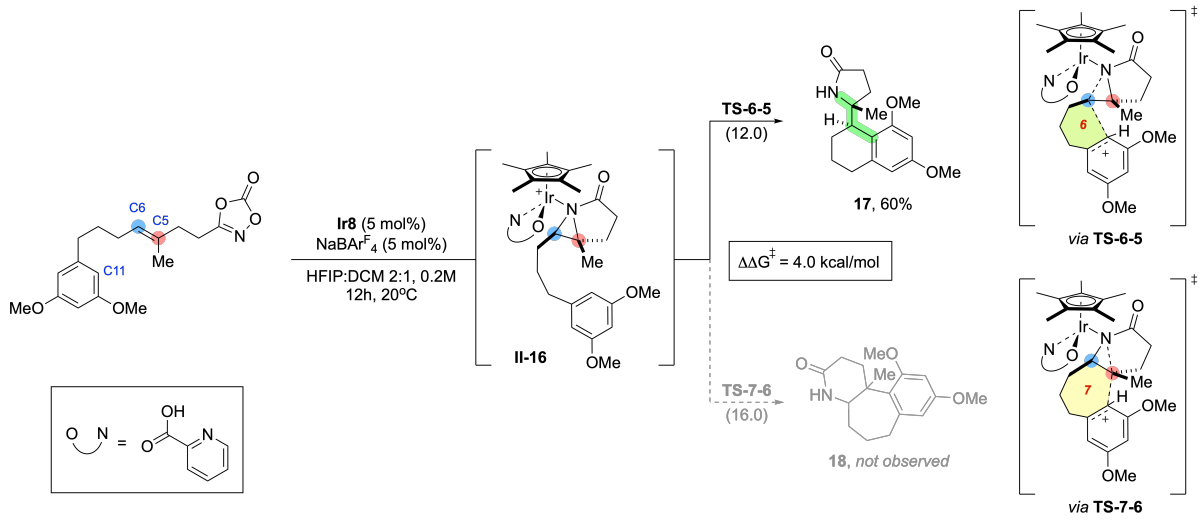


Figure 2. Experimental mechanistic investigations using modified substrates. Computational level: SMD(HFIP:DCM=2:1)-B3LYP-D3/6-311+G**|SDD(Ir)//B3LYP-D3/6-31G**|LANL2DZ(Ir).

The intermediacy of aziridine in the present cascade cyclization was additionally examined by applying an elongated substrate **16**, wherein an additional methylene linker is present between the aryl moiety and olefin (Figure 2). When **16** was subjected to the reaction conditions containing **Ir8** catalyst, tetrahydronaphthalene-substituted γ-lactam **17** was formed exclusively in 60% yield, while a tricyclic δ-lactam **18** was not observed from the reaction mixture. This experimental observation is consistent with the computational analysis, where the barrier to access **17** via **TS-6-5** is 4.0 kcal/mol lower than that leading to the isomeric **18**. The observed selectivity in the aziridine opening of **II-16** can be attributed to the geometrical preference for the six-membered ring transition state (**TS-6-5**) over the seven-membered transition state (**TS-7-6**).

CONCLUSION

In conclusion, we have disclosed the first example of the cascade cyclization reaction of olefinic aryl dioxazolones to furnish ring-fused *δ*-lactam products in a highly diastereoselective manner. This ring-closure reaction was elucidated to initiate via an intramolecular transfer of the *in situ* generated electrophilic Ir-acylnitrenoids to the neighboring alkenyl group to lead to a key *N*-acylaziridine intermediate. Subsequent intramolecular ring-opening by terminating pendant (hetero)arenes or alkynes was shown to proceed in high regioselectivity to produce ring-fused δ-lactams, and no γ-lactam derivatives were formed. This biomimetic cascade cyclization is expected to find its immediate applications in synthetic chemistry and medicinal/materials science, especially to increase the molecular diversification of available condensed azacyclic compounds of high utility.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting Information, with procedures, characterization for all the compounds, computational details, DFT studies on the elongated substrate **16**, cartesian coordinates and XRD data (PDF)

Collection of all the NMR spectra and chromatograms (PDF)

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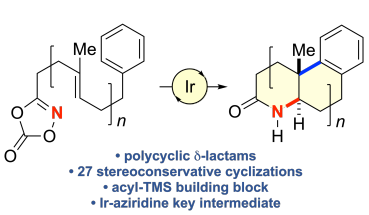
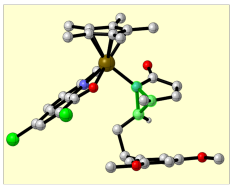
TOC



• polycyclic δ-lactams
• 27 stereoconservative cyclizations
• acyl-TMS building block
• Ir-aziridine key intermediate



Ir-aziridine intermediate