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Copper-Catalyzed Asymmetric Nitrenoid Transfer to Access Fused δ-Lactams via HFIP-Assisted Aziridination and Cascade Cyclization

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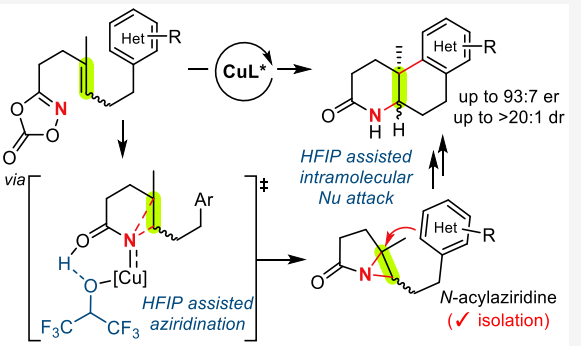
ABSTRACT: Aza-steroids and terpenoid alkaloids are prominent entities of biorelevant ring-fused azacycles with significant pharmaceutical applications. Despite their importance, synthetic approaches to these complex molecules remain a great challenge due to the lack of strategic routes to the multiple contiguous chiral centers, particularly in the case of thermodynamically unstable *cis*-ring frameworks. Herein, we report a Cu-catalyzed asymmetric cascade cyclization of arylalkenyl dioxazolones to access ring-fused δ-lactams. It is initiated to form a bicyclic *N*-acylaziridine intermediate to involve a concerted transition state, allowing an asynchronous C−N bond formation on the open-shell singlet surface. This key reactivity is enabled by 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), which stabilizes the reactive Cu-acylnitrenoid intermediate via inner-sphere hydrogen bonding. The resulting *N*-acylaziridine undergoes HFIP-promoted regio- and diastereoselective ring-opening with pendant arene or heteroarene nucleophiles to deliver condensed δ-lactam products with excellent *anti*-selectivity.



INTRODUCTION

Aza-steroids and terpenoid alkaloids constitute a captivating class of biorelevant ring-fused azacycles with diverse pharmacological applications (Scheme 1a).[1−5] For instance, they include therapeutics such as Izonsteride, a 5α-reductase inhibitor widely used in the treatment of benign prostatic hyperplasia and male pattern hair loss.[6,7] In addition, terpenoid alkaloids, biosynthetically assembled through cyclase-mediated nitrogen incorporation, feature prominent examples including ergot alkaloids, which exhibit dual roles as natural toxins and pharmaceutical agents.[8−10]

Despite their biological and synthetic significance, the construction of aza-polycycles remains a formidable challenge, primarily due to the need for precise control over multiple contiguous stereocenters, including demanding quaternary carbon centers.[11] These issues are further amplified especially when targeting *cis*-fused frameworks, where maintaining *cis*-ring junctions is inherently difficult.[12−14] Thus, there is a pressing demand for innovative methodologies that can address these obstacles, ideally through rapid and stereoselective polycyclization approaches from readily available prochiral polyene substrates.

Polyene cyclization stands as a hallmark example of a biomimetic transformation successfully translated from nature to synthetic laboratories.[5,15] Extensive investigations over the past decades have unveiled key mechanistic features of this process, ranging from the biosynthetic logic of terpene assembly to the stereoelectronic principles governing selectivity.[16−19] Although Stork and Eschenmoser independently proposed foundational stereoelectronic models for polyene cyclizations more than 70 years ago,[20,21] enantioselective variants of these cascades have only begun to emerge in recent years.[22] Nonetheless, most current strategies depend on carbocationic intermediates, inherently restricting their scope to hydrocarbon frameworks.[14,23−28]

Moreover, the initiation of biomimetic cyclizations at heteroatom sites, particularly nitrogen, remains largely unexplored, presenting a significant opportunity for the construction of ring-fused heterocycles. Previously, we reported an iridium-acylnitrenoid-initiated biomimetic cascade cyclization enabling the racemic synthesis of polycyclic δ-lactams (Scheme 1b).[29] This strategy leveraged a proposed bicyclic *N*-acylaziridine intermediate, which was assumed to undergo subsequent intramolecular nucleophilic ring-opening to construct a δ-lactam framework with complete diastereoselectivity. Nevertheless, critical challenges still remain: (i) use of precious metal, (ii) limited scope toward *cis*-decahydroquino-

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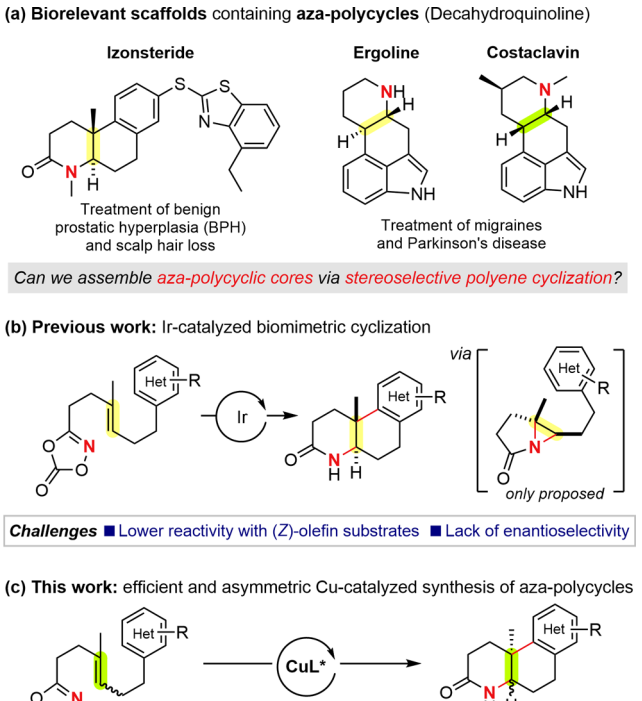
Scheme 1. Synthetic Challenges in Aza-Polycyclization



line frameworks, and (iii) the absence of enantioselective aza-polycyclization.

Recognizing that this cyclization relies on nitrenoid initiation, we turned our attention to other nitrene systems as potential alternatives.[30−32] Extensive studies on Fe,[33−37] Co,[38−42] Cu,[43−46] Ru,[47,48] and Ag[49−51] catalysts have established the versatility of metal−nitrenoid chemistry in engaging alkenes and other unsaturated systems across a broad range of transformations. These investigations have elucidated both concerted and stepwise nitrene transfer pathways and highlighted the critical role of metal−ligand combinations in controlling reactivity and selectivity.[52−54] However, catalytic systems that integrate such nitrenoid reactivity into complex enantioselective polycyclization cascades remain underdeveloped.

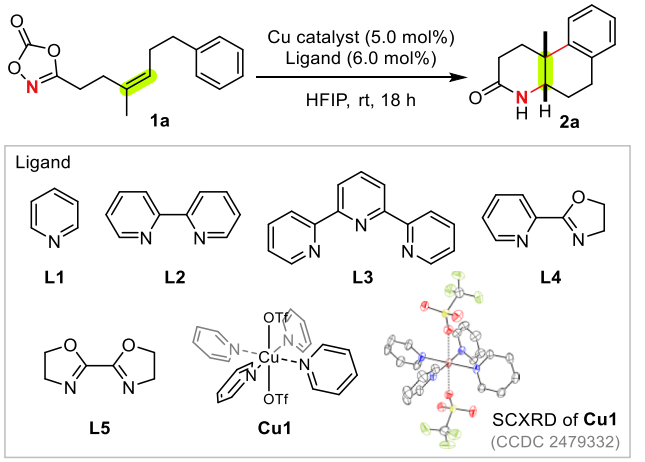
Given these issues, we envisaged that copper catalysis would present an attractive solution owing to its earth abundance, cost-effectiveness, and unique reactivity profile.[55−61] Prior works demonstrated that copper catalysis could allow efficient aziridination reactions while preserving substrate geometry, notably generating *cis*-aziridines from *cis*-alkenes.[62,63] Moreover, the copper catalysts paired with chiral bis(oxazoline) or diamine ligands have shown significant promise for asymmetric induction.[64−66] These attributes, combined with copper's environmental advantages and versatility, position it as an ideal candidate for the development of an asymmetric aza-polycyclization method, which will be described herein (Scheme 1c).

RESULTS AND DISCUSSION

Development of Copper-Catalyzed Reactions. Inspired by the pioneering works of Evans[62,63] and Jacobsen[65,66] on copper-catalyzed aziridination of (*Z*)-olefin substrates, we initiated our investigation by evaluating various copper species in combination with diverse ligands to assess their effectiveness in promoting aza-polycyclization via an electrophilic nitrenoid transfer.[43−46,67,68] Dioxazolones, which can be readily prepared in two steps from the corresponding carboxylic acids, are well-established as versatile and efficient nitrene precursors, rendering them particularly suitable for this study.[69−76] Recognizing the critical importance of controlling both the initiation and propagation steps in a cascade cyclization, we designed phenyl-tethered (*Z*)-alkenyl dioxazolone **1a** as a model substrate to probe whether a biomimetic polycyclization could be triggered through *in situ* generation of a highly reactive nitrenoid intermediate, eventually furnishing the desired polycyclic product **2a** (Table 1).

Initial screening of copper salts and ligands revealed that $Cu(OTf)_2$ in the presence of pyridine ligand **L1** efficiently promoted the transformation, affording the desired product **2a**

Table 1. Optimization of Cu Catalysts toward Cascade Cyclization[a]



Entry	Cu catalyst	Ligand	RSM[b] (%)	2a[b] (%)	rr[b]
1[c]	$Cu(OTf)_2$	**L1**	n.d.	73	>20:1
2	$Cu(OTf)_2$	**L2**	n.d.	n.d.	-
3	$Cu(OTf)_2$	**L3**	57	n.d.	-
4	$Cu(OTf)_2$	**L4**	n.d.	9	-
5	$Cu(OTf)_2$	**L5**	n.d.	n.d.	-
6[c]	$Cu(NTf_2)_2$	**L1**	n.d.	73	>20:1
7[c]	$CuBr_2$	**L1**	n.d.	58	>20:1
8	**Cu1**	-	n.d.	75	>20:1
9	$Cu(OTf)_2$	-	n.d.	n.d.	-
10	-	-	>95	n.d.	-

[a]Reaction conditions: **1a** (0.1 mmol), Cu source (5.0 mol%), and ligand (6.0 mol%) in HFIP (0.5 mL) at room temperature for 18 h. [b]Yields and regioselectivities (rr) were determined based on the ^{1}H NMR analysis of the crude reaction mixture using 1,1,2-trichloroethane (0.1 mmol) as an internal standard. [c]12 mol% of ligand was used. RSM = remaining starting material. n.d. = not detected.

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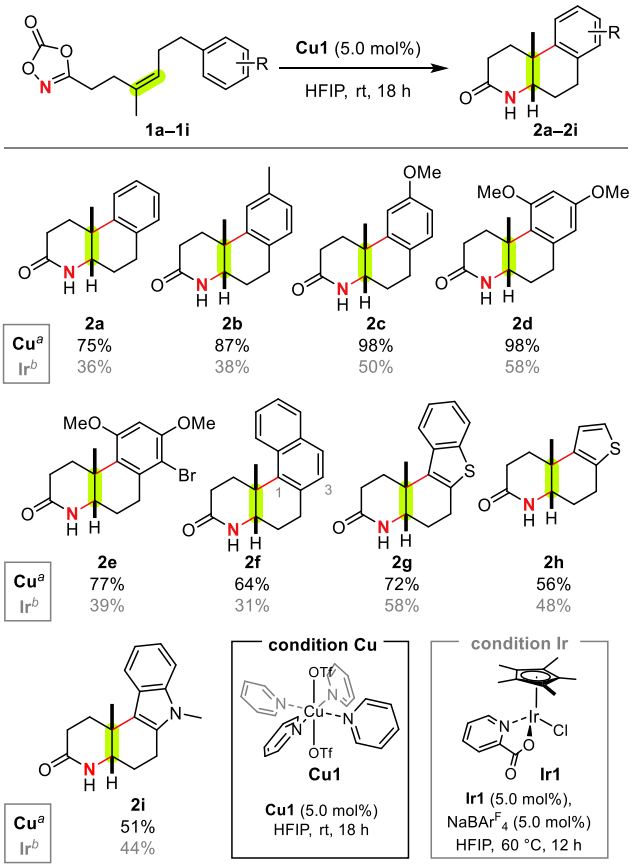
in 73% yield with excellent regioselectivity (>20:1 rr; entry 1). In contrast, ligands **L2**–**L5** were largely ineffective, either resulting in no observable product formation or providing only trace yield (entries 2–5), thus highlighting the critical role of ligand structure in achieving effective nitrenoid transfer and subsequent cyclization. Comparable efficiencies were also observed when $Cu(NTf_2)_2$ or $CuBr_2$ were employed with **L1** (entries 6 and 7, respectively), albeit with slightly lower yields.

Notably, tetrakis(pyridine)copper(II) triflate (**Cu1**), a readily accessible copper source,[77−80] also proved effective, delivering the desired product in 75% yield with high regioselectivity (entry 8). As anticipated, no product formation was observed in the absence of either the copper source or the ligand (entries 9 and 10, respectively), demonstrating the necessity of both components for promoting this transformation. Screening of other solvents revealed significantly diminished reactivity compared to the optimized conditions (further details are provided in the Supporting Information).

Reaction Scope of Cu-Catalyzed Polycyclization. With the optimized catalytic conditions in hand, we evaluated the substrate scope of the copper-catalyzed cascade cyclization using (*Z*)-configured dioxazolones **1a**–**1i** bearing various aryl-terminating groups and benchmarked its performance against our previously reported Ir-catalyzed system (Table 2).[29] The

Table 2. Cyclization Scope of (*Z*)-Olefinic Dioxazolone Substrates[ab]



[a]Reaction conditions: substrate (0.1 mmol) and **Cu1** (5.0 mol%) in HFIP (0.5 mL) at room temperature for 18 h. Unless otherwise stated, polycyclic *δ*-lactams were obtained in >10:1 dr. [b]Reaction conditions: substrate (0.1 mmol), **Ir1** (5.0 mol%), and NaBAr$^F_4$ (5.0 mol%) in HFIP (0.5 mL) at 60 °C for 12 h.

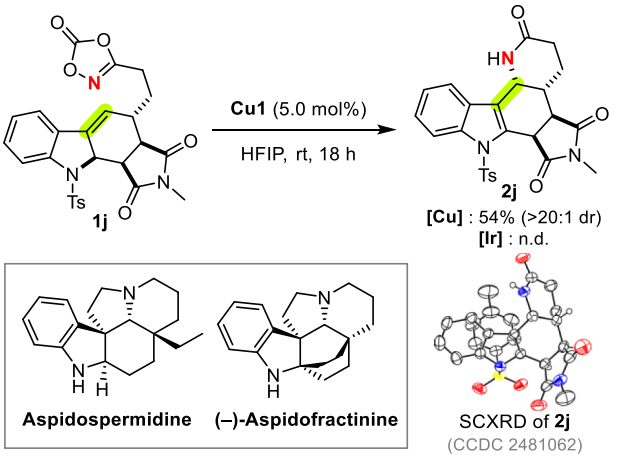
polycyclization of (*Z*)-olefinic aryl dioxazolones was proposed to proceed via a tightly organized chair-like transition state, consistent with the Stork–Eschenmoser hypothesis,[20,21,81] wherein the initial alkene geometry dictates the relative stereochemistry of the products.

For the model substrate **1a**, the Cu-catalyzed system afforded 75% yield of the desired product **2a**, markedly superior to the 36% yield obtained under the Ir catalysis. Likewise, a variety of (*Z*)-(aryl)alkenyl dioxazolones bearing electronically modified aryl groups underwent more efficient cyclization, delivering the corresponding products (**2b**–**2f**) in good to excellent yields with high diastereoselectivity. Substrates featuring *para*-substituents such as methyl (**1b**) and methoxy (**1c**) groups again demonstrated notable enhancements, providing the desired products in 87% and 98% yields, respectively, compared to only 38% and 50% yields under the Ir conditions. In particular, the *meta*-dimethoxy-substituted phenyl substrate (**1d**) underwent smooth cyclization, furnishing the product **2d** in >95% yield.

A densely functionalized bromophenol substrate (**1e**) also proved compatible, yielding the decahydroquinolinone product in 77% yield to offer an opportunity for downstream diversification via cross-coupling strategies. A substrate bearing a naphthalene moiety (**1f**) was cyclized effectively under Cu-catalyzed conditions, maintaining high yields and excellent regioselectivity. Notably, nucleophilic attack occurred exclusively at the C1 position of the naphthalene ring, despite the potentially competing reactivity at C3, indicating remarkable positional selectivity. Furthermore, heteroaryl-containing substrates, including benzothiophene, thiophene, and *N*-methylindole derivatives, readily underwent cyclization under copper catalysis, affording the desired products (**2g**–**2i**) with significantly improved yields. Overall, the copper catalyst consistently outperformed the Ir-based system across a broad range of substrates, underscoring its operational simplicity, wide substrate scope, and capability for constructing *cis*-decahydroquinoline frameworks.

Encouraged by the broad applicability, we extended the methodology to a more structurally complex system (Scheme 2). Specifically, we targeted a densely fused substrate featuring a [6.5.6.6.5] pentacyclic framework reminiscent of Aspidospermidine, a monoterpenoid indole alkaloid renowned for its synthetic complexity and biological significance.[82,83] Notably,

Scheme 2. Synthesis of Aspidospermidine Core Structures



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it encompasses four contiguous stereocenters and serves as a prototypical member of the Aspidosperma alkaloid family, comprising over 250 bioactive compounds.[84,85]

Despite numerous synthetic endeavors since Stork's landmark total synthesis in 1963,[86] catalytic strategies enabling efficient access to the Aspidospermidine core have remained underdeveloped, primarily due to the severe steric congestion and electronic intricacy of the framework.[87,88] Notably, our previously reported Ir-catalyzed system failed to cyclize substrates of this type, yielding no detectable products under standard conditions.

In sharp contrast, the current Cu-catalyzed protocol successfully enabled the formation of the highly fused pentacyclic product **2j** in a synthetically useful yield. The structure of **2j** was unambiguously confirmed by X-ray crystallographic analysis, which highlights the unique reactivity and superior functional group tolerance of the Cu-based system, establishing it as an effective platform for accessing complex alkaloid architectures.

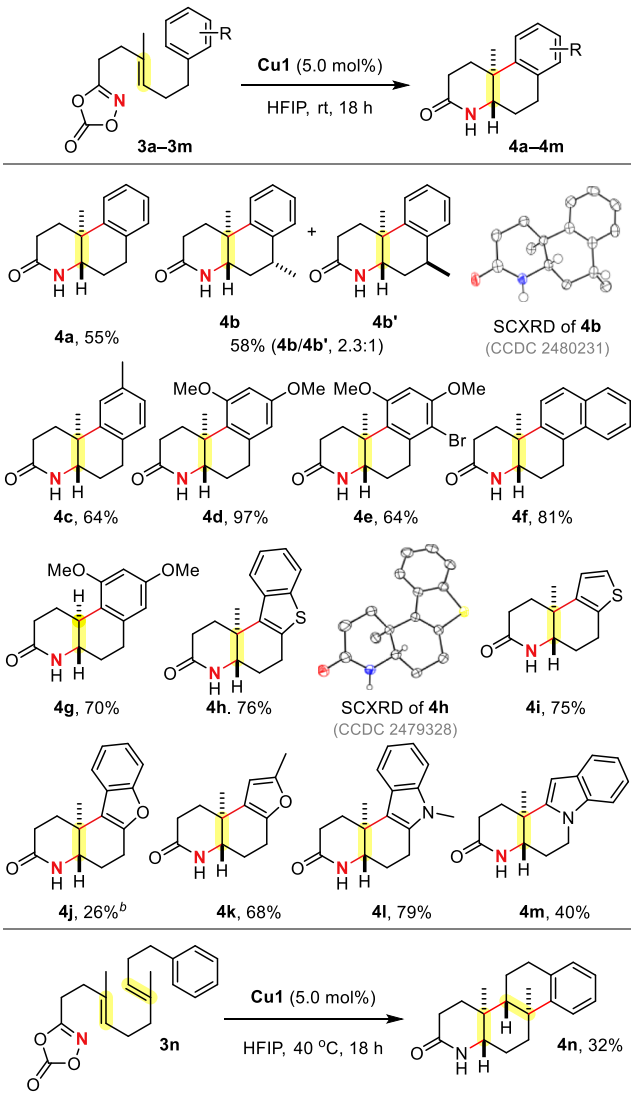
Following the optimization with (*Z*)-configured substrates, we next explored the cyclization of (*E*)-configured dioxazolones **3a**−**3m** bearing various aryl-terminating groups (Table 3). A wide array of arene substituents, including substituted phenyl (**3a**−**3e**) and naphthyl (**3f**) moieties, engaged effectively in the nitrenoid-initiated biomimetic cyclization, affording the corresponding products in good yields. However, substrates containing a methyl group adjacent to the phenyl ring (**3b**) exhibited moderate diastereoselectivity (2.3:1 dr), and the major diastereomer was isolated and structurally confirmed by X-ray crystallographic analysis. To further probe the impact of alkene substitution, we evaluated substrate **3g**, which lacks a methyl group on the alkene. The reaction proceeded smoothly under standard conditions, delivering cyclized product **4g** in 70% isolated yield, thus reinforcing the robustness and generality of the developed protocol.

In addition, a broad range of heteroaryl-containing substrates was observed to be compatible under the optimized conditions without requiring solvent modifications, such as the use of nonafluoro-*tert*-butanol (NFTB). In fact, (benzo)-thiophene, (benzo)furan, and indole derivatives underwent efficient cyclization, producing the desired polycyclic products (**4h**−**4m**) in consistently high yields. These findings further attest to the operational flexibility and versatility of the Cu-catalyzed aza-polycyclization approach.

Building on the successful dicyclization of arylalkenyl dioxazolones, we next investigated a tricyclization using the bis-olefinic substrate **3n**. We envisioned that copper-mediated acylnitrenoid transfer to the proximal olefin would initiate the cascade process, forming a bicyclic aziridine intermediate that could further undergo sequential intramolecular cyclizations with the remote olefin and tethered aryl group. Under the optimized conditions, (*E*,*E*)-configured diolefinic substrates (**3n**) delivered the tetracyclic products (**4n**) in 32% yield. Notably, a single diastereomer bearing four contiguous stereocenters was obtained, highlighting the high stereocontrol of the transformation.

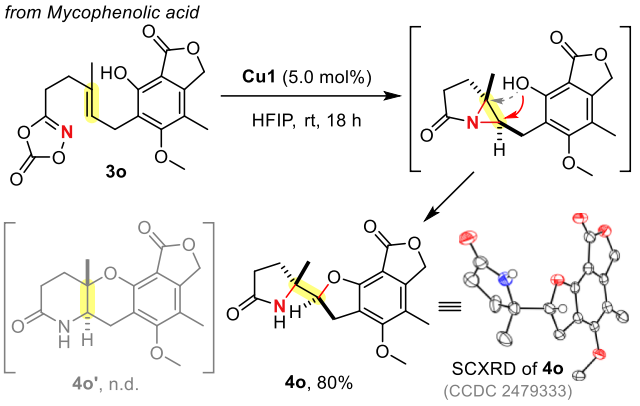
To expand the nucleophile scope, we prepared dioxazolone substrate **3o** from mycophenolic acid in two steps (Scheme 3). This substrate features a shortened linker, lacking one methylene unit between the aryl ring and the olefin, and bears an *ortho*-hydroxyl group on the aromatic ring. Under the **Cu1**-catalyzed conditions, the phenolic hydroxyl group was found to act as an internal nucleophile, undergoing cyclization

Table 3. Cyclization Scope of (*E*)-Olefinic Dioxazolone Substrates[a]



[a]Reaction conditions: substrate (0.1 mmol) and **Cu1** (5.0 mol%) in HFIP (0.5 mL) at room temperature for 18 h. Unless otherwise stated, polycyclic *δ*-lactams were obtained in >10:1 dr. [b]Performed an acid workup.

Scheme 3. Cu-Catalyzed Cascade Cyclization Using Phenol as Internal Nucleophile



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to afford γ-lactam **4o** incorporating a dihydrobenzofuran motif as a single product in 80% yield; notably, the competing tetracyclic δ-lactam **4o′** was not observed. SCXRD analysis confirmed the γ-lactam structure and revealed *anti*-selectivity, providing strong evidence for an aziridine involvement in the reaction pathway.[89−91] These results suggest that 5-membered ring closure is favored over 6-membered ring formation, presumably due to conformational constraints imposed by the substrate geometry.

Development of Asymmetric Reactions. To extend the methodology into a new version of asymmetric aza-polycyclization, we turned our attention to copper-catalyzed nitrene transfer processes by examining various chiral ligands.[64−66] An (*E*)-configured phenylalkenyl dioxazolone substrate (**3a**) was selected as a model substrate to evaluate the feasibility of an enantioselective biomimetic cascade cyclization (Table 4). Initial screening focused on Cu(I) sources in combination with a range of *N,N*-type bidentate chiral ligands. Reactions were carried out using $Cu(MeCN)_4BF_4$ in HFIP and different ligand systems. The catalytic outcomes revealed that the ligand structure had a pronounced influence on the reaction efficiency as well as enantioselectivity, while the *trans*-diastereoselectivity remained relatively consistent across different conditions.

Employing a methylene-bridged bis(oxazoline) ligand (BOX, **L*1**) resulted in the formation of the tricyclic δ-lactam product **4a** almost in a racemic form (49:51 er) with moderate yield (39%), although diastereoselectivity was still excellent (15:1 dr). Subsequent evaluation of alternative ligand classes revealed that a pyridine−oxazoline ligand (PyOx, **L*2**) slightly improved both the chemical yield and enantioselectivity (65:35 er). Meanwhile, the use of a pyridine−bis(oxazoline) ligand (PyBox, **L*3**) furnished the cyclized product **4a** in 56% yield with higher enantioselectivity (30:70 er), whereas diastereoselectivity was significantly decreased (7.0:1 dr).

Notably, the bis(oxazoline) ligand lacking a linker (BiOx, **L*4**) proved more effective, affording the polycyclic product **4a** in 56% yield with excellent diastereoselectivity (>20:1 dr) and more improved enantioselectivity (78:22 er). Motivated by these encouraging results, we systematically modified the phenyl substitution of the BiOx ligand to probe the effect of steric and electronic variations. The introduction of an electron-withdrawing CF_3 group at the *para*-position (**L*5**) led to reduced enantioselectivity and diminished reactivity relative to that of **L*4**. Conversely, the installation of an electron-donating methoxy group (**L*6**) slightly enhanced the enantioselectivity.[92] By contrast, increasing the steric bulkiness on the ligand backbone (**L*7**) provided a pronounced improvement in enantioselectivity (88:12 er) while maintaining high reactivity, indicating that steric effects are the dominant factor in this system. A full summary of ligand optimization is provided in the Supporting Information.

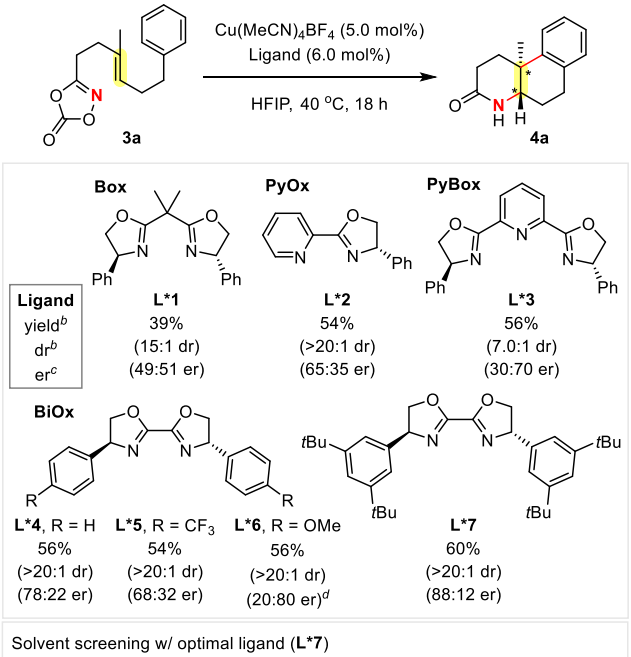
The reaction efficiency also displayed a notable dependence on the solvent employed. In nonpolar solvents such as dichloromethane (DCM) and chlorobenzene (PhCl), no δ-lactam product **4a** was detected. Likewise, protic solvents, including methanol (MeOH), isopropyl alcohol (*i*-PrOH), phenol (PhOH), and nonafluoro-*tert*-butanol (NFTB), failed to furnish the desired product. Trifluoroethanol (TFE) afforded only a trace amount of **4a**. In sharp contrast, only HFIP enabled the reaction to proceed efficiently, and its specific role will be discussed in detail in the mechanistic section (*vide infra*).

Reaction Scope of Cu-Catalyzed Asymmetric Aza-Polycyclization. Having established effective conditions for the asymmetric cascade cyclizations, we next investigated the generality of this approach using (*E*)-configured dioxazolone substrates bearing various aryl terminal groups (Table 5). A variety of arenes, including substituted phenyl (**4a**, **4c**−**4e**) and naphthyl (**4f**) derivatives, smoothly participated as terminating nucleophiles in the copper-catalyzed nitrenoid-initiated cyclization.

Of particular interest, a substrate bearing a densely substituted bromophenol moiety underwent the cascade process efficiently, furnishing the decahydroquinolinone product **4e** in 69% yield with a 72:28 er. Furthermore, single-crystal X-ray diffraction analysis of the recrystallized product **4e** unambiguously established its (*S,S*) absolute configuration and *trans*-fused geometry, demonstrating the *anti*-selectivity originating from the proposed aziridination mechanism.[47,93−95] Across the substrate set, the cascade cyclization consistently afforded *trans*-fused decahydroquinolinones in synthetically useful yields and as single diastereoisomers with moderate to high enantioselectivity.

To further investigate the impact of alkene substitution, we prepared disubstituted (*E*)-olefinic substrate **3g**, in which the methyl group on the alkene backbone was omitted. Under a slightly elevated reaction temperature (60 °C) and extended reaction time (48 h), the desired cyclized product **4g** was

Table 4. Optimization of Chiral Cu Catalysts toward Asymmetric Cascade Cyclization[a]



[a]Reaction conditions: **3a** (0.1 mmol), $Cu(MeCN)_4BF_4$ (5.0 mol%), and ligand (6.0 mol%) in HFIP (2.5 mL) at 40 °C for 18 h. [b]Yields and regioselectivities (rr) were determined based on the ^1H NMR analysis of the crude reaction mixture using 1,1,2-trichloroethane (0.1 mmol) as an internal standard. [c]Enantiomeric ratio (er) was determined by chiral HPLC. [d]The opposite enantiomer was used. [e]PhOH/DCM (1:1) was used as the cosolvent.

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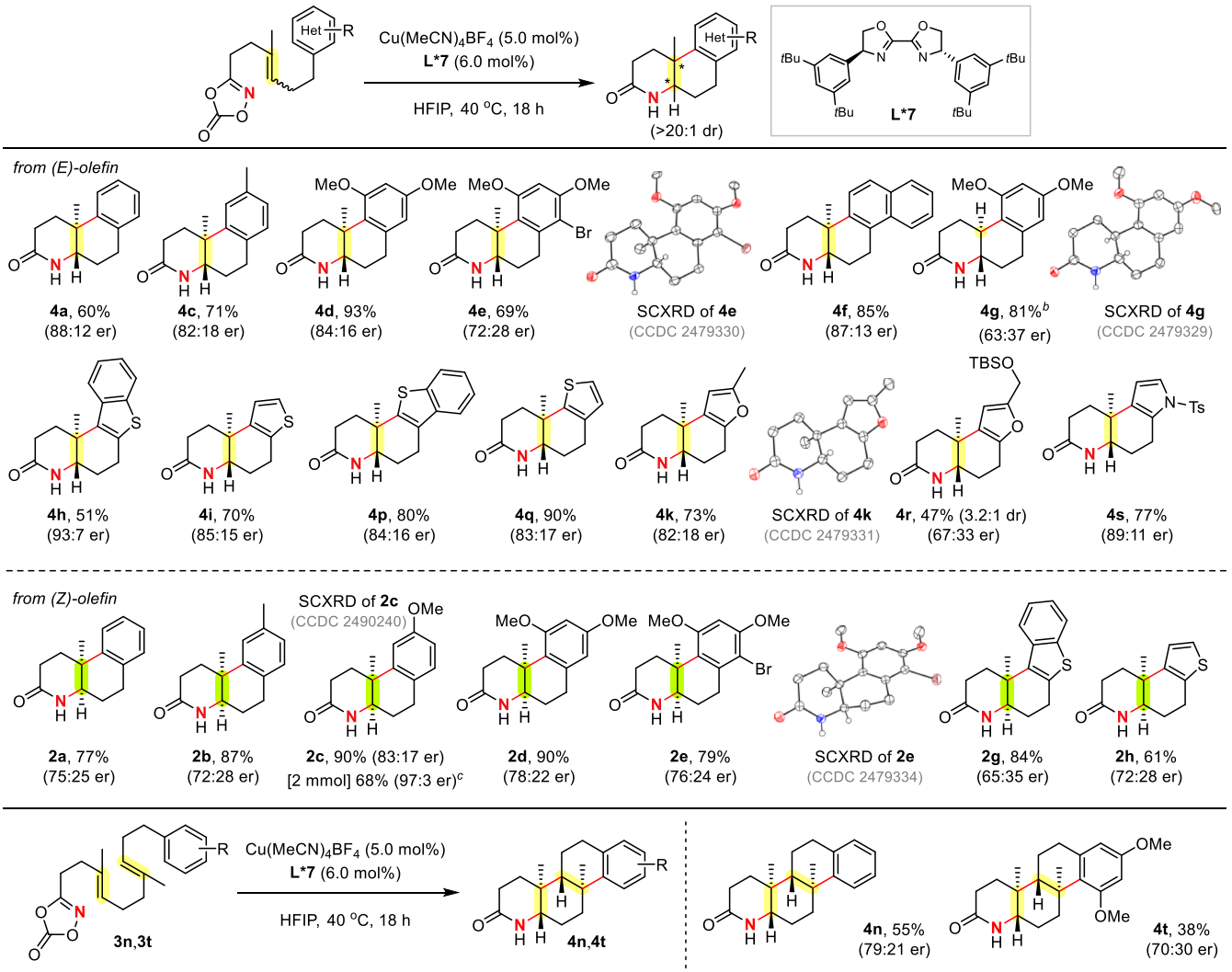
Table 5. Substrate Scope for the Asymmetric Cu-Catalyzed Polycyclizations[a]



[a]Reaction conditions: dioxazolone (0.1 mmol), $Cu(MeCN)_4BF_4$ (5.0 mol%), and **L*7** (6.0 mol%) in HFIP (2.5 mL) at 40 °C for 18 h. Unless otherwise stated, polycyclic *δ*-lactams were obtained in >20:1 dr. [b]Under 60 °C for 48 h. [c]After recrystallization.

obtained in 81% isolated yield, albeit with a diminished enantiomeric ratio of 63:37. This outcome suggests that the methyl substituent may contribute to enantiodiscrimination, likely by influencing the steric environment of the transition state—a hypothesis further supported by DFT calculations (*vide infra*).

In contrast, substrates bearing electron-withdrawing substituents, such as chloro or bromo groups at the *para*-position of the aromatic ring, were unreactive under the standard conditions. Instead, monocyclized enamide products were predominantly formed, even when employing elevated temperatures and increased catalyst loadings. These observations suggest that a diminished electron density on the aryl ring hampers the sequential cyclization pathway.

In addition to (*E*)-aryl-substituted substrates, heterocyclic olefinic dioxazolones were also evaluated to further demonstrate the versatility of the copper-catalyzed asymmetric cascade cyclization (Table 5). Electron-rich heteroaryl groups, including (benzo)thiophene, furan, and pyrrole, were successfully incorporated as nucleophilic terminators, affording the corresponding heterocycle-fused decahydroquinolinones in good to excellent yields and varied enantioselectivities.

Among the heterocycles evaluated, 2-benzo[*b*]thiophene-derived product **4h** exhibited the highest enantioselectivity (93:7 er). 2-thiophene-substituted substrate also performed well, affording the cyclized product in high yield with good enantioselectivity (**4i**). 3-benzo[*b*]thiophene derivative provided product **4p** in 80% yield and 84:16 er, while the 3-thiophene substrate delivered **4q** (90%) with comparable enantioselectivity. In the case of 2-methylfuran, substrate **3k** engaged smoothly in the cascade cyclization. By contrast, the 2-furan-derived substrate **3r**, bearing an O-*tert*-butyldimethylsilyl (OTBS) substituent, yielded the cyclized product (**4r**) with moderate diastereoselectivity (3.2:1 dr) and low enantioselectivity (67:33 er), presumably due to the steric and conformational effects of the OTBS substituent. The pyrrole-containing substrate furnished its corresponding product (**4s**) with an 89:11 er. Collectively, these results highlight the broad applicability of the copper-catalyzed protocol across a wide range of heterocyclic substrates, while revealing distinct selectivity trends governed by the electronic and structural features of the nucleophilic heteroaryl groups.

Following the successful development of *trans*-selective cyclization with (*E*)-olefinic substrates, we additionally

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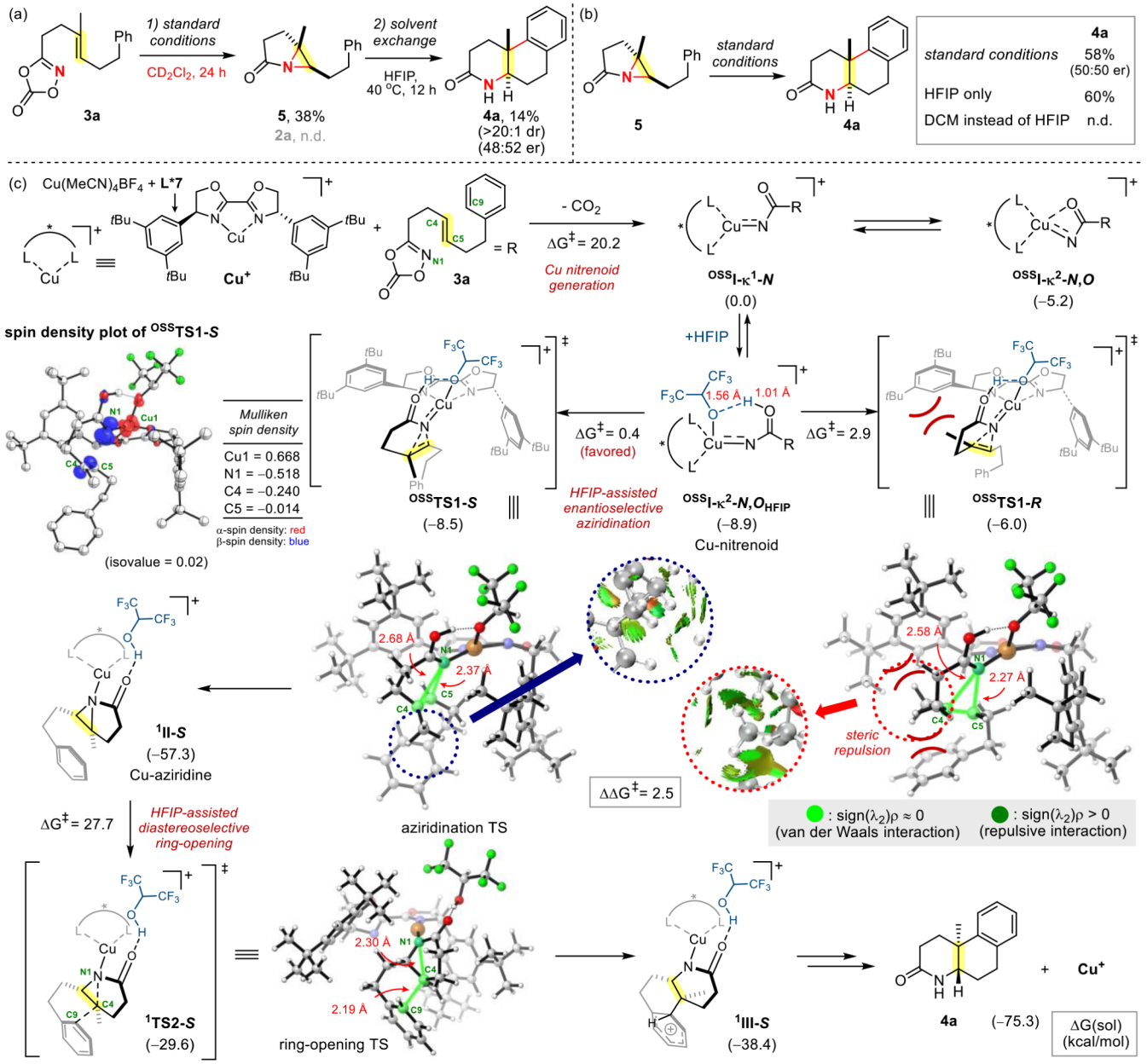

Figure 1. (a) Observation of *N*-acylaziridine intermediate 5. (b) HFIP-promoted ring-opening of aziridine intermediate 5. (c) DFT computational study of Cu-nitrenoid-mediated cascade cyclization. Computational level: SMD(HFIP)-(U)ωB97XD/def2tzvpp//SMD(HFIP)-(U)ωB97XD/def2svpldef2tzvpp(Cu). See the Supporting Information for the aziridine ring-opening process in HFIP only.

investigated whether (*Z*)-configured dioxazolones could also participate in the asymmetric cascade reaction to access the *cis*-fused decahydroquinolinone framework. Pleasingly, (*Z*)-substrate **1a** exclusively afforded the *cis*-fused product (**2a**) in 77% yield, with excellent diastereoselectivity (>20:1 dr), albeit in moderate enantioselectivity (75:25 er), under the optimized conditions. Additional (*Z*)-olefinic substrates containing electronically modified aryl groups, as well as heteroarenes such as (benzo)thiophenes, were similarly well tolerated, yielding cyclized products (**2b**−**2e**, **2g**, and **2h**) with moderate to high diastereo- and enantioselectivity. X-ray diffraction of the bromine- and dimethoxy-substituted products **2e** confirmed the assigned relative and absolute configuration. It is noteworthy that Ir-catalyzed systems showed markedly diminished reactivity toward (*Z*)-olefinic substrates, while the Cu-catalyzed protocol readily accommodated even electron-rich heterocycles, thereby significantly broadening the accessible structural space.

To highlight the scalability and synthetic utility of this method, the cyclization of **1c** was successfully performed on a 2 mmol scale, delivering the desired product (**2c**) in 77% isolated yield with an 83:17 er. Furthermore, recrystallization of the crude product enhanced the enantiopurity to a 97:3 er, with a 68% isolated yield. This performance proves the practicality of the current Cu-catalyzed system for preparative-scale synthesis of enantioenriched *cis*-fused heterocycles.

Building on these results, we next examined the feasibility of asymmetric tricyclization reactions using bisolefinic dioxazolones. To our satisfaction, (*E*,*E*)-diolefinic phenyl dioxazolones **3n** and **3t** underwent smooth tricyclization under the optimized conditions, delivering tetracyclic products (**4n** and **4t**, respectively) in satisfactory yields, albeit with moderate

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enantioselectivity. In both cases, a single diastereomer was obtained, featuring four newly generated contiguous stereogenic centers. This exceptional diastereoselectivity underscores the precise control achieved in the tricyclization process and further highlights the potential of the copper catalysis system for the efficient construction of complex, densely fused polycyclic architectures.

Mechanistic Investigations. To probe the reaction mechanism, we first examined the role of HFIP in the reaction. Solvent screening of the asymmetric Cu-catalyzed polycyclization (Table 4) showed that HFIP is essential as a solvent for this transformation. A series of protic solvents with diverse pK_a values (MeOH, *i*-PrOH, TFE, NFTB, and PhOH) were tested, but only HFIP (pK_a = 9.3)[96] efficiently promoted the desired cyclization. Notably, even phenol, which possesses a comparable pK_a value (9.95),[97] failed to afford the product. These findings indicate that HFIP does not act merely as a simple Brønsted acid. Instead, its unique effectiveness presumably arises from a combination of factors, in particular its reduced nucleophilicity and strong hydrogen bond-donating ability, which together enable effective stabilization of cationic intermediates.[98−100] These features are known to influence the reactivity of electrophilic nitrenes,[89−91,101,102] particularly in aziridination, and in some cases promote ring-opening processes such as those of epoxides[103,104]—an effect potentially relevant to our aziridine system. HFIP is also frequently employed in polycyclizations involving cationic intermediates.[26,28,29,105−107] Given these precedents, we next investigated the reaction outcome in the absence of HFIP.

A series of control experiments were first conducted (Figure 1). When the reaction was performed under the standard asymmetric conditions in CD_2Cl_2 instead of HFIP, starting material **3a** was converted to afford *N*-acylaziridine intermediate **5** in 38% crude yield, while no polycyclic product **4a** was detected. This intermediate, previously proposed but not experimentally confirmed, was directly observed in this experiment, supporting its involvement in the reaction pathway. After removal of CD_2Cl_2 and subsequent addition of HFIP to the same reaction mixture, the polycyclic product was obtained in 14% yield with excellent diastereoselectivity (>20:1 dr), but nearly racemic enantioselectivity (48:52 er), despite the presence of a chiral ligand **L*7**. These results suggest that HFIP plays a crucial role in enabling asymmetric induction in aziridination and facilitates the postulated nucleophilic ring-opening.

To further elucidate the role of HFIP in the ring-opening event, racemic *N*-acylaziridine intermediate **5** was independently synthesized (see Supporting Information) and subjected to the standard asymmetric conditions, affording polycyclic product **4a** in 58% yield. However, the resulting product was obtained in racemic form, and no residual **5** was detected, thereby excluding the possibility of kinetic resolution during the sequential cyclization pathway. A comparable yield (60%) was also achieved when the reaction was conducted in HFIP as the solvent without a catalyst and ligand. In contrast, when DCM was used instead of HFIP, polycyclic product **4a** was not formed, and 44% of aziridine intermediate **5** remained unreacted. These findings indicate that HFIP can promote aziridine ring-opening and subsequent cyclization, even in the absence of a copper catalyst system.

To complement these experimental findings and elucidate the origin of enantioselectivity, DFT calculations were carried out using the optimal catalyst system $[Cu(MeCN)_4]BF_4$, chiral ligand **L*7**, and (*E*)-configured substrate **3a** (Figure 1c). The reaction is initiated by coordination of dioxazolone **3a** to the ligated cationic copper(I) species $\mathbf{Cu}^+$, followed by decarboxylation to generate the key Cu-acylnitrenoid intermediate **I**, with a calculated activation barrier of 20.2 kcal/mol (see Supporting Information for details). Consistent with our model, Cu−nitrenoid species have frequently been proposed as reactive intermediates in nitrene transfer reactions.[44−46,67,68,108,109]

A set of spin states (singlet, triplet, and open-shell singlet), along with plausible coordination geometries (κ^1-*N*, κ^2-*N*,*O*, and κ^2-*N*,O_{HFIP} binding modes), were evaluated for intermediate **I**.[68,108,110−112] Among these, the most stable configuration was identified as the HFIP-bound open-shell singlet ^{OSS}**I**-$\boldsymbol{\kappa}^1$-*N*,O_{HFIP}, which lies significantly lower in energy than either the three-coordinate ^{OSS}**I**-$\boldsymbol{\kappa}^1$-*N* (ΔG = +8.9 kcal/mol) or the four-coordinate ^{OSS}**I**-$\boldsymbol{\kappa}^2$-*N*,*O* (ΔG = +3.7 kcal/mol). This HFIP adduct suggests a possible inner-sphere interaction of HFIP with the metal center.[113] In this HFIP adduct, the distance between the carbonyl oxygen of the acylnitrenoid and the HFIP hydrogen is approximately 1.01 Å, while the O−H bond length in HFIP is elongated to 1.56 Å, consistent with a geometry approaching protonation of the carbonyl group. This suggests the presence of strong inner-sphere hydrogen bonding (Supporting Information).

The enantio-determining step is proposed to involve the aziridination of the tethered olefin by the HFIP-bound Cu−nitrenoid intermediate. This step features the formation of two C−N bonds in a concerted but asynchronous manner, proceeding via a single transition state located on the open-shell singlet surface. In the optimized structure of ^{OSS}**TS1**-*S*, the N1−C5 bond is more advanced (2.37 Å) than the N1−C4 bond (2.68 Å), highlighting the asynchronous nature of bond formation, with a nearly barrierless activation energy ($\Delta G^{\ddagger}$ = 0.4 kcal/mol). Among the computed transition structures, ^{OSS}**TS1**-*S* was found to be 2.5 kcal/mol more stable than ^{OSS}**TS1**-*R*, in good agreement with the experimentally observed (*S*,*S*)-enantioselectivity (Table 5).

Structural analysis of these transition states suggests that the enantioselectivity originates from differential steric repulsion between the substrate and the ligand environment. In ^{OSS}**TS1**-*R*, a methyl substituent on the alkene experiences unfavorable steric interactions with a phenyl group of the ligand. In contrast, in ^{OSS}**TS1**-*S*, these repulsions are alleviated by the downward reorientation of the ligand backbone, resulting in a spatial arrangement more favorable for aziridination. Noncovalent interaction (NCI) analysis supports this steric model, revealing enhanced repulsive contacts in the *R*-configurated transition state.[114] Consistent with this model, substrate **3g**, lacking the methyl substituent, furnished product **4g** with lower enantioselectivity (63:37 er, Table 5) than substrate **3a**, which delivered product **4a** with 81:19 er under identical conditions (60 °C, Table S3).

In addition, Mulliken spin density analysis of ^{OSS}**TS1**-*S* indicates unpaired electron density localized on the copper center (0.668 α), the nitrene nitrogen (−0.518 β), and the alkene carbons C4 (−0.240 β) and C5 (−0.014 β), consistent with substantial diradical character.[115] This electronically asynchronous, concerted transition state—critically stabilized by HFIP—accounts for both the observed reactivity and stereochemistry. Moreover, the synchronous setting of two stereocenters within a single well-defined transition structure

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likely underlies the consistently high diastereoselectivity across diverse substrates.

From aziridine intermediate ^{1}**II**-*S*, the pendant aromatic ring acts as an internal nucleophile to form the polyfused *δ*-lactam (**4a**). Nucleophilic attack by the aryl carbon (C9) at the aziridine carbon (C4) occurs via a 6-membered-ring transition state (^{1}**TS2**-*S*), leading to the formation of a Wheland intermediate (^{1}**III**-*S*) with an activation barrier of 27.7 kcal/mol.[116] In ^{1}**TS2**-*S*, the forming C9−C4 bond and breaking N1−C4 bond are characterized by distances of 2.19 and 2.30 Å, respectively, indicating a concerted S_N2-like ring-opening process. This step proceeds with high stereoselectivity and furnishes the polycyclic *δ*-lactam product **4a** upon rearomatization of ^{1}**III**-*S*, accompanied by the regeneration of cationic copper species **Cu**$^+$. Notably, both the copper catalyst and HFIP may contribute as Lewis acids to activate the aziridine ring toward nucleophilic attack. Furthermore, experimental results (Figure 1b) show that aziridine ring-opening can occur solely in the presence of HFIP. This HFIP-promoted activation mode aligns with a previous report[103] describing its role in facilitating nucleophilic ring-opening processes (see the Supporting Information).

CONCLUSIONS

In this study, we have newly developed a biomimetic Cu-catalyzed asymmetric cascade cyclization of arylalkenyl dioxazolones, enabling highly regioselective and stereoselective access to condensed azacyclic scaffolds. This protocol accommodates a broad range of aryl and heteroaryl substrates, demonstrating excellent substrate generality. Mechanistic studies, supported by both experimental observations and DFT calculations, reveal that the key aziridination step proceeds via an electronically asynchronous yet concerted transition state on the open-shell singlet surface. This transformation is critically facilitated by HFIP, which stabilizes the reactive Cu-acylnitrenoid species through inner-sphere hydrogen bonding. The resulting *N*-acylaziridine intermediate, isolated and characterized, subsequently undergoes regio- and diastereoselective ring-opening to furnish chiral *δ*-lactams bearing fused-ring architectures. The combined experimental and computational insights highlight the pivotal role of both HFIP and open-shell Cu-nitrenoid character in steering the reaction with high selectivity. Overall, this work offers a powerful and mechanistically informed strategy for constructing complex nitrogen heterocycles relevant to natural product synthesis and drug discovery.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c14319.

Experimental procedures, characterization of new compounds, computational details, Cartesian coordinates of computed structures, and crystallographic information (PDF)

Accession Codes

Deposition Numbers 2479328−2479334, 2480231, 2481062, and 2490240 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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