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Synthesis of Stereoselective Multifused Cyclic Compounds via Palladium-Catalyzed C3-Allylative Dearomatization

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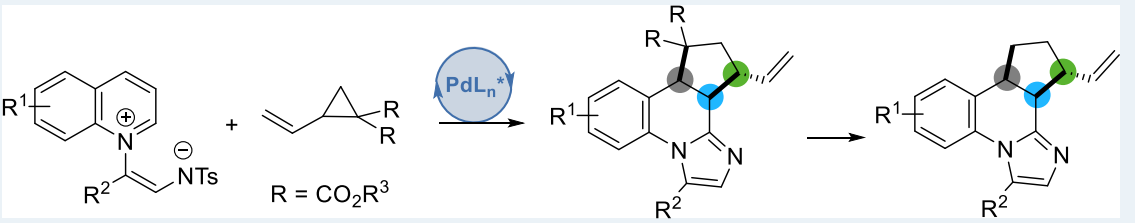

ABSTRACT: In this study, Pd-catalyzed enantioselective C3-allylative dearomatization is performed, which proceeds via dearomative [3 + 2] cycloaddition involving quinolinium zwitterions and vinyl cyclopropanes. This protocol is significant for the synthesis of complex, multifused cyclic compounds characterized by meticulously controlled multistereogenic centers using π-allyl palladium species. The method developed herein presents an approach to overcoming the challenge of achieving stereoselective C3-functionalization. The SEGPHOS ligand plays an integral role in this process by improving both the conversion rates and stereoselectivity. Our investigation also underscores the versatility of this methodology by demonstrating its potential for the construction of stereocontrolled fused *N*-cyclic systems. The results of this study lay the foundation for the further exploration and refinement of asymmetric dearomatization aimed at the strategic construction of stereoselective *N*-heterocyclic compounds.

KEYWORDS: *heterocycles, dearomatization, cycloaddition, stereoselectivity, palladium catalyst*

Fused heterocyclic compounds play a pivotal role in natural products, pharmaceuticals, and biologically active molecules (Figure 1).[1] The structural diversity of these compounds is indispensable in the early stages of drug discovery and the development of novel functional compounds. Nevertheless, the synthesis of these fused heterocyclic compounds poses formidable challenges, primarily stemming from the precise control of stereoselectivity and the effective management of their intricate molecular structures. This complexity is further compounded by the presence of multiple stereocenters, rendering their syntheses even more challenging.

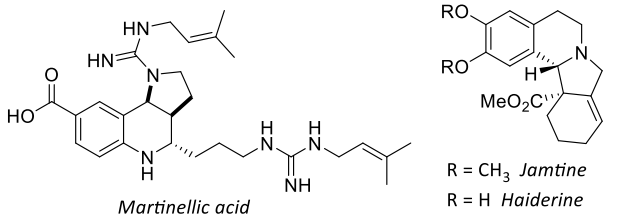

Figure 1. Stereoselective fused heterocyclic skeletons in biologically active molecules.

One promising strategy for constructing intricate cyclic compounds involves dearomative functionalization using *N*-heteroarenes.[2] This approach is particularly attractive for synthesizing complex fused-ring compounds and has demonstrated its practical utility across applications in various fields. In previous studies, the predominant focus has been the exploration of the C2- or C4-functionalization of activated *N*-heteroarenes, driven by the distinctive electronic properties intrinsic to these compounds.[3] This field has seen considerable advancement with the development of the so-called Wenkert procedure, which not only showcased the multifunctionalization of *N*-arenium salts but also demonstrated its utility in synthesizing natural products (Scheme 1A).[4] Subsequently, an antithetical approach has emerged, redirecting attention toward the challenging process of dearomative functionalization at the C3 position of *N*-arenium salts (Scheme 1B).[5] While the Wenkert procedure introduces a functional group at the C4 position of the *N*-arenium species to generate a dihydropyridine intermediate, the antithetical method commences with the formation of a similar intermediate via the 1,4-dearomative reduction of *N*-arenium. A subsequent Stork-type reaction of dihydropyridine, followed by an additional reduction, facilitated the introduction of a functional group at

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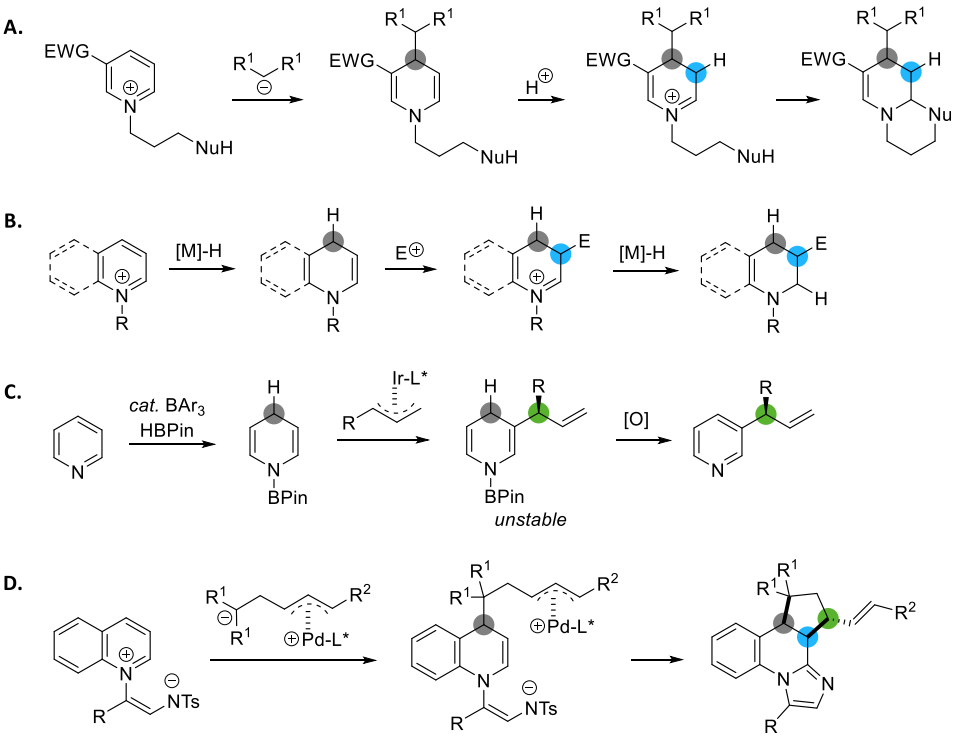
Scheme 1. Regio- and Stereoselective Functionalization of *N*-Aromatic Compounds: (A) Dearomative Multifunctionalization of *N*-Arenium Salts; (B) Dearomative C3-Functionalization of *N*-Arenium Salts; (C) Asymmetric C3-Allylation of *N*-Arenes; (D) Asymmetric C3-Allylative Dearomatization of *N*-Arenium Zwitterions (this work)

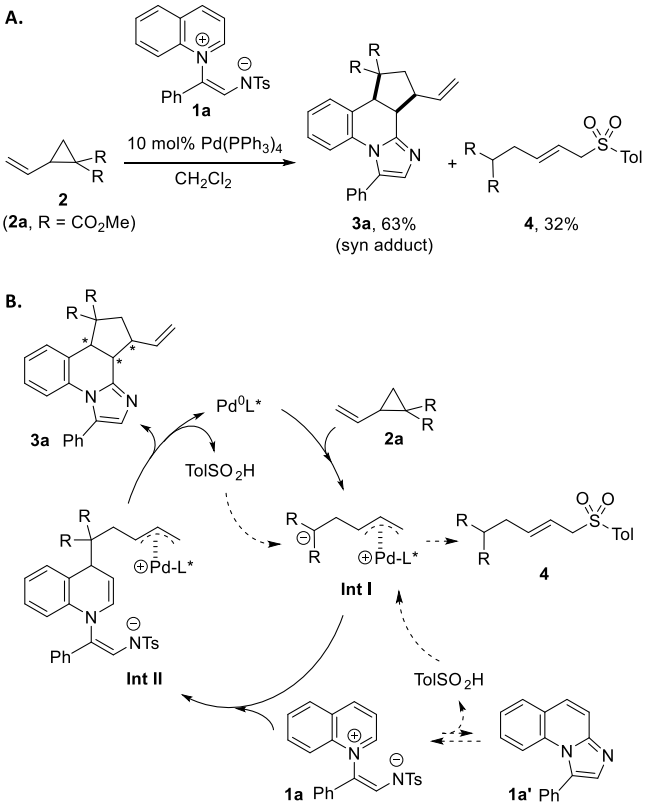


the C3 position. Nevertheless, the asymmetric version of this methodology remains unexplored. In a more straightforward approach, the most recent advancement involves the asymmetric C3-allylation of unactivated *N*-heteroarenes,[6] which employs boron-containing Lewis acid catalysis to achieve regioselective 1,4-dearomative hydroboration, followed by asymmetric allylation at the C3 position of dihydropyridine intermediates, ultimately affording efficient stereoselective C3-allylative pyridines (Scheme 1C).

We have previously proposed a series of dearomative cycloaddition methodologies, focusing on the functionalization of activated *N*-heteroarenes.[7] Building upon our previous findings, we envisioned that orchestrating a stereoselective cycloaddition between activated *N*-heteroarenes and metal-bound π-allyl species could simultaneously govern both asymmetric allylation and stereogenic configuration of the homoallylic carbon within the fused-ring system. In this study, we performed a catalytic cycloaddition reaction involving activated *N*-heteroarenes and Pd-bound π-allyl species, thereby facilitating the construction of intricate sterically complex molecules while simultaneously achieving precise stereoselective control over multiple chiral carbons (Scheme 1D).

Initially, vinyl cyclopropane (**2**) was thoughtfully selected as a precursor capable of reacting regioselectively at the C4 position of activated *N*-heteroarenes bearing π-allyl groups in the presence of Pd(0) catalyst (Scheme 2).[8] Subsequently, we investigated its reactivity in terms of cycloaddition with the quinolinium zwitterion (**1a**) and explored the potential for achieving precise control over the formation of consecutive stereogenic centers in the [3 + 2] cycloaddition product (**3a**). First, we explored the reactivity of vinyl cyclopropanes (**2**) bearing various electron-withdrawing functional groups, including ketones, esters, amides, and nitriles. Only **2a**, bearing

Scheme 2. Palladium-Catalyzed Cycloaddition of Quinolinium Zwitterion and Vinyl Cyclopropane: (A) Cycloaddition of Quinolinium Zwitterion and Vinyl Cyclopropane; (B) Plausible Mechanism of [3 + 2] Cycloaddition and Undesired Pathway



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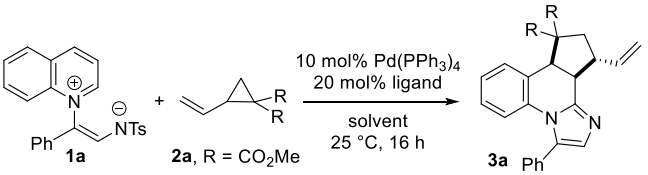
an ester substituent at R, demonstrated some reactivity, furnishing the desired cycloadduct **3a** (63%) (Scheme 2A). Despite the formation of a substantial quantity of the byproduct, viz. allylic sulfone **4**, the expected outcome, i.e., formation of the ring in the desired compound **3a** via syn-addition, was observed.[9] Despite the presence of multiple stereogenic carbon centers within the product, only a pair of enantiomers (**3a**) was observed. This selectivity is governed by the thermodynamic preference for the cis configuration at the ring junction during pentagonal ring formation, which is intricately correlated to the stereoselective placement of the allyl functional group. This observation inspired us to explore the potential for obtaining precise control over contiguous stereogenic configurations in a single operation by employing compatible chiral ligands in the [3 + 2] dearomative cycloaddition.

To enhance the stereoselectivity, we envisioned a refined reaction mechanism aimed at optimizing the reactivity while minimizing undesirable side reactions. As illustrated in Scheme 2B, the catalytic cycle commenced with the oxidative addition of Pd(0) to **2a**, forming Intermediate I (**Int I**), which then selectively underwent 1,4-dearomative addition with the quinolinium zwitterion (**1a**), affording Intermediate II (**Int II**). The desired product is synthesized via the intramolecular allylation at the C3 position of *N*-heteroarene **1a**, involving the cyclization of Pd-bound π-allyl tethered **Int II**. Notably, toluenesulfinic acid ($TolSO_2H$) is generated as a byproduct of this transformation, along with the concurrent regeneration of the Pd(0) catalyst. Consequently, the isolated byproduct **4** can be ascribed to the nucleophilic addition of toluenesulfinic acid to **Int I**.[10] Additionally, trace amounts of toluenesulfinic acid may also be formed via the intramolecular cyclization of a quinolinium zwitterion (**1a**), thereby forming allylic sulfone **4**.

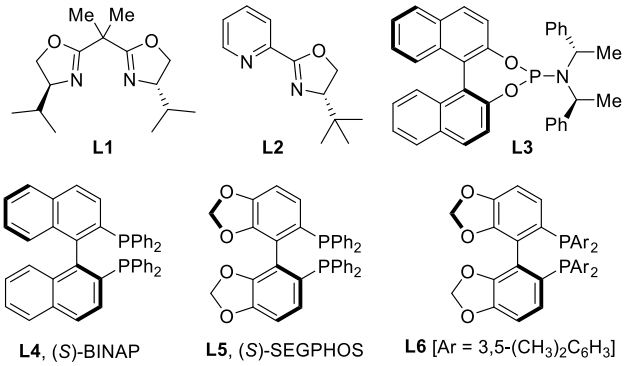
With an approach based on such mechanistic insight, we attempted to develop an asymmetric reaction between *N*-aromatic zwitterions and vinyl cyclopropanes for constructing fused cyclic compounds with multiple stereogenic centers (Table 1). In our initial experimental setup, we reacted the quinolinium zwitterion (**1a**) with vinyl cyclopropanes (**2a**) bearing various ligands in the presence of a catalytic amount of $Pd(PPh_3)_4$ and employed CH_2Cl_2 as the solvent. In the first nonasymmetric reaction, the electron-rich $P(p\text{-}OMePh)_3$ ligand notably enhanced the formation of the product (**3a**), affording an exceptional yield of 93% (entry 1). However, in this instance, an unintended byproduct (**4**) also emerged, with an isolated yield of 60%, owing to the addition of excess vinyl cyclopropane **2a**. Subsequently, we screened *N*,*N*-bidentate Box-type ligands, specifically **L1** and **L2**, which also enhanced the reaction yields. However, the corresponding product (**3a**) lacked stereoselectivity (entries 2 and 3). The (*S*,*S*,*S*)-MonoPHOS ligand **L3** yielded an intriguing result; it did not influence stereoselectivity despite affording slightly better yields (entry 4). This observation was unexpected because the phosphoramidite-type ligands have a well-established reputation for asymmetric reactions involving Pd-bound π-allyl species generated from vinyl cyclopropanes.[11] The encouraging observation is that the generation of byproduct **4** can be effectively mitigated by the implementation of a chiral ligand. In all instances involving the utilization of chiral ligands, compound **4** was not obtained. Fortunately, a turning point emerged when we introduced bidentate (*S*)-BINAP (**L4**) as the chiral ligand. This change produced the desired product (**3a**) in a 67% yield with a promising 73% ee (entry 5). Further

Table 1. Optimization Studies for the Enantioselective C3-Allyl Dearomatization[a,b]



entry	ligand	solvent	yield (%)[c]	ee (%)[d]
1	$P(p\text{-}OMePh)_3$	CH_2Cl_2	93	
2	**L1**	CH_2Cl_2	73	
3	**L2**	CH_2Cl_2	95	
4	**L3**	CH_2Cl_2	76	
5	**L4**	CH_2Cl_2	67	73
6	**L5**	CH_2Cl_2	98	91
7	**L6**	CH_2Cl_2	75	76
8	**L5**	1,4-dioxane	72	54
9	**L5**	THF	73	69
10	**L5**	Toluene	76	58
11[e]	**L5**	CH_2Cl_2	84	86
12	(*R*)-SEGPHOS	CH_2Cl_2	84	−91

[a]



[b]Conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), $Pd(PPh_3)_4$ (10 mol %), ligand (20 mol %), CH_2Cl_2 (4 mL), 25 °C, 16 h. [c]Isolated yields. [d]Enantiomeric excess was determined by HPLC. [e]The reaction mixture was stirred at 0 °C.

refinement was achieved using (*S*)-SEGPHOS (**L5**) as the ligand, characterized by a more electron-rich backbone than (*S*)-BINAP. Both the yield and stereoselectivity of the desired **3a** product were significantly improved to 98 and 91% ee, respectively, upon using L5 as the ligand (entry 6). Interestingly, the introduction of **L6**, characterized by a significantly bulkier environment than **L5**, led to a simultaneous reduction in both the yield (75%) and the enantiomeric excess (76%) (entry 7). Various solvents, including dioxane, THF, and toluene, were explored to fine-tune the reaction conditions. Regrettably, varying the solvent led to slightly lower yields and enantiomeric excesses (entries 8−10). Unexpectedly, the stereoselectivity was found to decrease slightly (86% ee) when the reaction was conducted at 0 °C (entry 11). Consequently, we confirmed that performing the reaction at room temperature with **L5** as the ligand provided the optimum results. Finally, the effect of ligand chirality was validated using (*R*)-SEGPHOS as the ligand, which afforded the enantiomer of product **3a** in an excellent yield with excellent enantiomeric excess (entry 12). The stereochemical configuration of the resulting compound (**3a**) was clearly determined via X-ray diffraction analysis of a single-crystal

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molecule.[12] As illustrated in Figure 2a, the newly formed five-membered-ring skeleton, originating from the cyclopropane

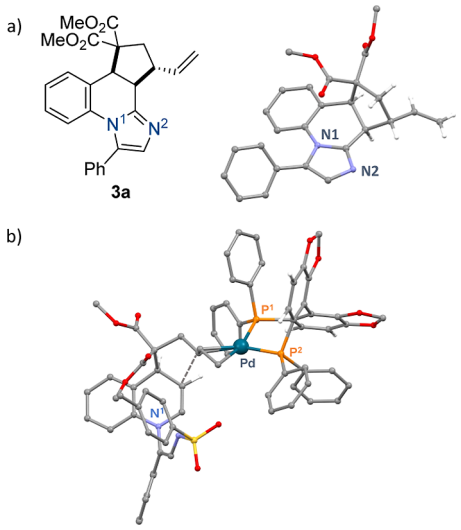

Figure 2. (a) X-ray crystal structure of **3a**. (b) Spatial proximity of predicted transition state in the stereodetermination step.

reactant, was situated perpendicular to the quinolinium backbone, while the stereochemistry of the vinyl functional group exhibited an antithetical orientation relative to the cyclic structure. Based on these structural insights, we anticipate that the transition state can control the cyclization of **Int II** (Figure 2b), which is a pivotal factor governing stereoselectivity. Pd chelated to the allyl moiety of **Int II** resides on the rear facet of the quinolinium backbone, guided by the chiral ligand (*S*)-SEGPHOS. This specific configuration guarantees the formation of a new ring in a *cis* configuration while simultaneously orienting the vinyl group on the opposite side of the ring.

Subsequently, we evaluated the broad applicability of the optimized enantioselective cycloaddition reaction (Scheme 3). In addition to the unsubstituted quinolinium zwitterion (**1a**), we systematically explored various quinolinium zwitterions (**1**) bearing substituents at diverse positions, all within the confines of the optimized reaction conditions when reacted with **2a**. Notably, the introduction of a methyl group at the C3 position of the quinolinium backbone, which can induce the formation of a quaternary carbon center in the product (**3b**), demonstrated a remarkable level of efficiency and exceptional selectivity in the asymmetric cycloaddition reaction. This led to the formation of the desired compound **3b** with an outstanding yield of 92% and with an exceptional enantiomeric excess of 99%. Conversely, the incorporation of substituents at the C6 position of the quinolinium scaffold, primarily influenced by their electronic properties, exerted a modest influence on the reaction, resulting in the synthesis of multifused *N*-heterocyclic compounds bearing chiral allylic functional groups (**3c**−**3h**). For example, the presence of primary and secondary alkyl substituents at the C6 position of **1** exhibited marginal influences on both reactivity and stereoselectivity, affording the desired products **3c** and **3d** in 73 and 72% yields, respectively, with enantiomeric excesses higher than 85%. The quinolinium zwitterion, bearing a methoxy group at position C6, exhibited noteworthy reactivity as it underwent conversion to compound **3e** in a 52% yield with a remarkable 91% ee. The incorporation of a silyl-protected alcohol functional group at the same position produced the cycloadded product **3f** with an impressive enantiomeric excess of 92%, albeit with a slightly diminished reaction yield. Moreover, zwitterions bearing electron-deficient fluoro- and chloro-substituents exhibited slower reactions with vinyl cyclopropane **2a**, affording the corresponding products **3g** and **3h** at enantiomeric excesses of 72 and 81%, respectively. Similarly, ester-substituted quinolinium zwitterion transformed into compound **3i** in a 59% yield with 70% ee under Pd-catalyst . The reduction in enantiomeric excess observed in electron-deficient substrates was postulated to result from the constrained nucleophilicity due to the electronic deficiency of the proposed **Int II** (Scheme 2B), which participates in the stereodetermining step. Interestingly, the methyl group at C7 did not significantly affect the selectivity of the reaction, affording **3j** in a 73% yield with a high enantiomeric excess of 90%. The reaction involving the 8-methoxy-substituted zwitterion proceeded smoothly, forming compound **3k** in an 80% yield with an impressive enantiomeric excess of 99%. Nonetheless, when employing pyridinium or isoquinolinium zwitterions as substrates under identical reaction conditions, it was noted that the intended stereoselective reaction did not transpire.

Next, we screened the enamide moiety of the zwitterion (**1**) for synthesizing the desired enantioselective cycloadducts (**3**). Specifically, a zwitterion substituted with a paramethylbenzene group as R^2 smoothly underwent conversion to the corresponding product (**3l**) with an impressive yield of 86% and an enantiomeric excess of 95%. Similarly, the presence of a *para-tert*-butylbenzene group as R^2 did not adversely affect the reactivity or selectivity, affording the corresponding product **3m** in an excellent yield of 98% and a commendable enantiomeric excess of 87%. However, the introduction of an electron-withdrawing *para*-fluoro substituent on the phenyl group of R^2 slightly affected the yield of product **3n** (83%) with an enantiomeric excess of 78%. When meta-substituents were incorporated into the benzene R^2 group of the zwitterion (**1**), the reaction exhibited little sensitivity to these modifications, producing the stereoselective products **3o**−**3q** in good yields and satisfactory stereoselectivity. While there were minor differences in the yields based on the specific substituent at the meta-position (methyl, methoxy, or fluoro), the enantiomeric excess remained consistent at ∼87% ee. However, for the zwitterion featuring two electron-deficient CF_3 substituents (**1r**), the reaction yield was notably diminished to 33%, and the enantiomeric excess was reduced to 60%, rendering it unsuitable for practical synthetic applications.

Variations in the structural composition of vinyl cyclopropane (**2**) were explored under well-defined optimized reaction conditions, yielding a diverse array of stereoselectively substituted fused-ring structures. Primary and secondary alkyl-ester-substituted vinyl cyclopropanes were particularly amenable to the enantioselective cycloaddition process, providing products **3s**, **3t**, and **3u** in robust yields of 83−90% and enantiomeric excesses of 81−86% ee.

Furthermore, the benzyl ester-substituted vinyl cyclopropane exhibited remarkable reactivity and readily participated in the cycloaddition with quinolinium zwitterion **1a**, generating the desired product **3v** in a commendable yield of 79% and an impressive enantiomeric excess of 85% ee. Conversely, the phenyl-substituted vinyl cyclopropane showed notable stereoselectivity (94% ee); however, the reaction yield decreased

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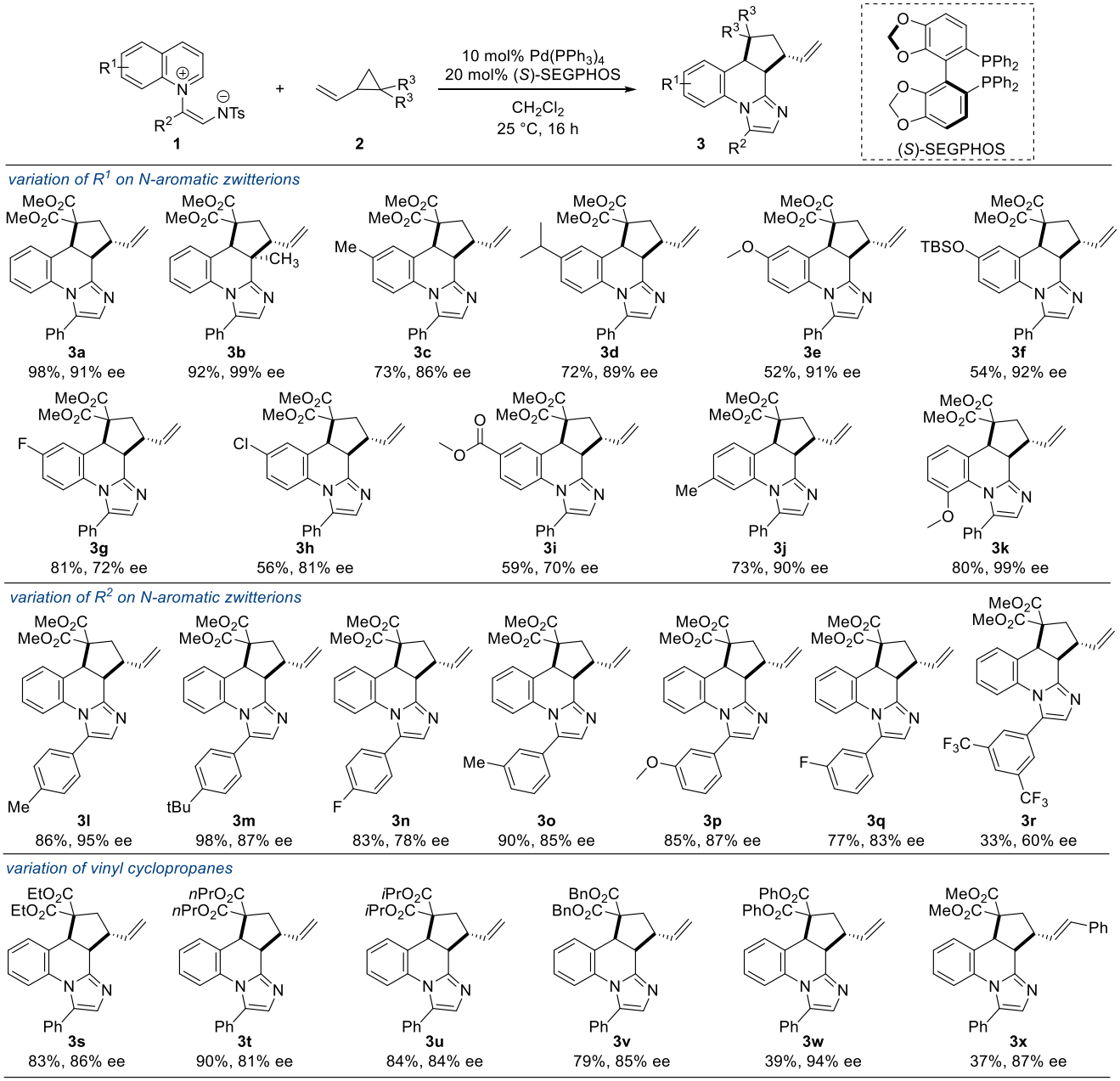
Scheme 3. Enantioselective Dearomative Cycloadditions between *N*-Aromatic Zwitterions and Vinyl Cyclopropanes[a,b]



[a]Conditions: **1** (0.2 mmol), **2** (0.5 mmol), $Pd(PPh_3)_4$ (10 mol %), (*S*)-SEGPHOS (20 mol %), CH_2Cl_2 (4 mL), 25 °C, 16 h. [b]Enantiomeric excess was determined by HPLC.

significantly. Similarly, vinyl cyclopropanes bearing a phenyl substituent at the vinylogous position exhibited limited reactivity, affording the desired compound **3x** in a modest yield (37%). Nevertheless, enantioselectivity remained high (87% ee). Regrettably, despite the application of our meticulously optimized reaction conditions, vinyl cyclopropane substituted with other electron-withdrawing groups, such as ketones, amides, nitriles, or sulfone moieties, remained unreactive, aligning with the outcomes of our initial reaction experiments.

The synthetic potential of this approach was assessed by performing scale-up experiments and various functionalization reactions (Scheme 4). Starting with **1a** (2.5 mmol), we achieved the gram-scale synthesis of **3a** with minimal impact on the yield or enantioselectivity. The vinyl functional group present in cycloadduct **3a** was successfully converted to a primary alcohol (**4**) via rhodium-catalyzed hydroboration and subsequent oxidation with hydrogen peroxide, affording the product in a high yield (81%) and enantiomeric excess (90%). Additionally, the chemoselective reduction proceeded smoothly, with the vinyl group being reduced selectively to produce **5** (95% yield, 91% ee) using a Pd/C catalyst and hydrogen gas. The ester in **3a** was easily transformed into the primary alcohol (**6**) with $LiAlH_4$ (87% yield, 87% ee).

Gratefully, we achieved the synthesis of decarbonylated compound **8** from standard product **3a** through a three-step conversion process. The use of NaCN was employed to remove an ester functional group via a radical pathway.[13] In a

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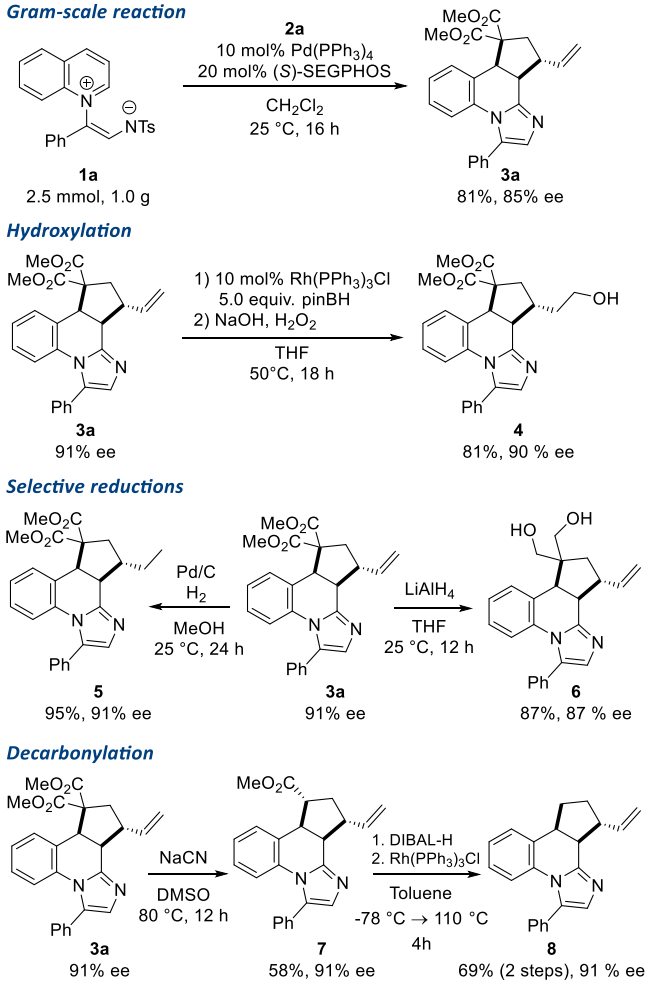
Scheme 4. Synthetic Applications



sequential fashion, we meticulously carried out a reduction utilizing DIBAL-H, followed by the Tsuji-Wilkinson decarbonylation of the resulting aldehydes using a rhodium catalyst.[14] Importantly, it was evident that the stereoselectivities of the multifused heterocyclic compounds, induced via these transformation processes, remained largely unaltered, underscoring the robustness of the methodology. By employing stepwise decarbonylation, we effectively broadened the formerly restricted substrate scope, specifically vinyl cyclopropanes, which had previously been limited to electron-withdrawing substituted variants. This approach not only extended the versatility of our developed reaction but also provided compelling evidence of its practical feasibility.

In summary, we have successfully developed a Pd-catalyzed enantioselective C3-allylative dearomatization method utilizing the dearomative [3 + 2] cycloaddition between quinolinium zwitterions and vinyl cyclopropanes. This method efficiently produces complex multifused cyclic compounds with well-arranged and consecutive stereogenic carbon centers. The crucial role played by the electron-rich SEGPHOS ligand, which contributes to rapid conversion and high stereoselectivity, cannot be overstated. Furthermore, we demonstrated the versatility of this approach in terms of additional stereoselective transformations, highlighting its potential for synthesizing fused *N*-cyclic systems with controlled multistereogenic centers that may serve as bioactive compounds and pharmacophores. Our ongoing research should expand the scope of asymmetric dearomatization by focusing on the construction of stereoselective *N*-heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c05058.

Experimental procedures and analytical data (PDF)

Crystallographic information for compound **3a** complex (CIF)

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Notes

The authors declare no competing financial interest.

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