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# Asymmetric Dearomative Cascade Multiple Functionalizations of Activated *N*-Alkylpyridinium and *N*-Alkylquinolinium Salts

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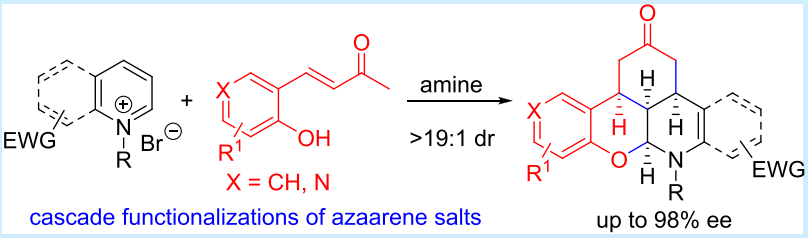


**ABSTRACT:** An enantioselective cascade reaction of *N*-alkylpyridinium and -quinolinium salts with *o*-hydroxybenzylideneacetones to access fused polyheterocycles through cross dienamine-mediated addition followed by trapping of the dearomatized enamine-type intermediates and aminal formation has been developed. A cascade assembly of *N*-benzyl-4-methylpyridinium salt and cyclic 2,4-dienones is further disclosed to give bridged frameworks via repetitive dearomatization and aromatization activation.



Nitrogen-containing fused and even polycyclic frameworks with three-dimensional architectures are ubiquitous in natural products and pharmaceutically important substances,[1] and thus, the development of asymmetric reactions to effectively access these drug-like hetero libraries triggers continuing interest in organic and medicinal chemistry.[2] Among them, the asymmetric dearomative reaction of azaarenes provides a versatile strategy to construct enantioenriched alkaloid compounds, and a diversity of elegant processes have been uncovered.[3] Nevertheless, examples of cascade multiple functionalizations[4] on the pyridine and quinoline skeletons still have been rarely reported, though some potentially reactive species would be usually generated during the dearomative process. In fact, *N*-alkylated pyridinium or quinolinium salts have been demonstrated to be highly active in a number of dearomative reactions, including asymmetric versions, through suitable nucleophilic additions. In contrast, most cases are still limited to furnishing relatively simple monofunctionalization of the azaarene ring at C2 or C4,[5] though the electron-rich enamine functionality, showing apparent nucleophilicity,[6] is formed in the dearomative products (Scheme 1a).

Recently, the Yoo group designed a type of pyridinium zwitterions that could be regioselectively assembled with palladium–trimethylenemethane (Pd-TMM) species, followed by intramolecular capture of the iminium ions (Scheme 1b).[7] Additionally, Bu and co-workers uncovered base-promoted multiple functionalizations of diverse *N*-alkyl azaarene salts that usually proceed by cascade C4- and C2-regioselective attack by bisnucleophilic enaminones, and sometimes the enamine intermediates could be captured by suitable electrophiles inter- or even intramolecularly (Scheme 1c).[8] Nevertheless, none of them have achieved the potential asymmetric control, though multiple stereogenic centers generally have been constructed in the products with high molecular complexity. To address such a deficiency, here we disclose previously unreported asymmetric dearomative cascade functionalizations of *N*-alkylpyridinium and -quinolinium salts with simple benzylideneacetones bearing an *o*-hydroxy group via aminocatalysis,[9] efficiently affording fused heterocyclic architectures with high levels of stereocontrol (Scheme 1d).

In our initial study, we explored the reaction between *N*-benzyl-3-cyanopyridinium salt **1a** (Table 1, $R^1$ = Bn) and *o*-hydroxybenzylideneacetone (**2a**) (Table 1, $R^2$ = $R^3$ = H, X = CH) under aminocatalytic conditions.[5k] It was pleasing that the cascade functionalization process took place as expected via tandem enamine/iminium ion activation, giving the fused tetracyclic framework **3a** as a single diastereomer. It should be noted that the final aminal formation is crucial for the cascade process, since only the dearomative addition step was observed for simple benzylideneacetone.[10] After investigation of a variety of catalytic parameters, product **3a** was obtained in 78% isolated yield with excellent enantioselectivity (98% ee) by employing quinine-derived primary amine **C1** (20 mol %)[11] and salicylic acid (**A1**) (20 mol %) in the presence of potassium salicylate (**B1**) (1.1 equiv), even on a larger scale. Subsequently, we examined the scope and limitations of this dearomative cascade reaction. *o*-Hydroxybenzylideneacetones **2** with a substituent at

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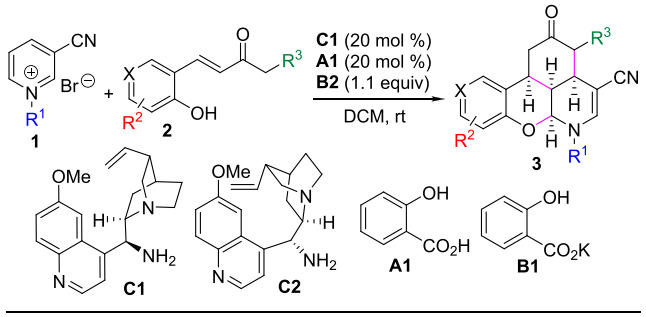
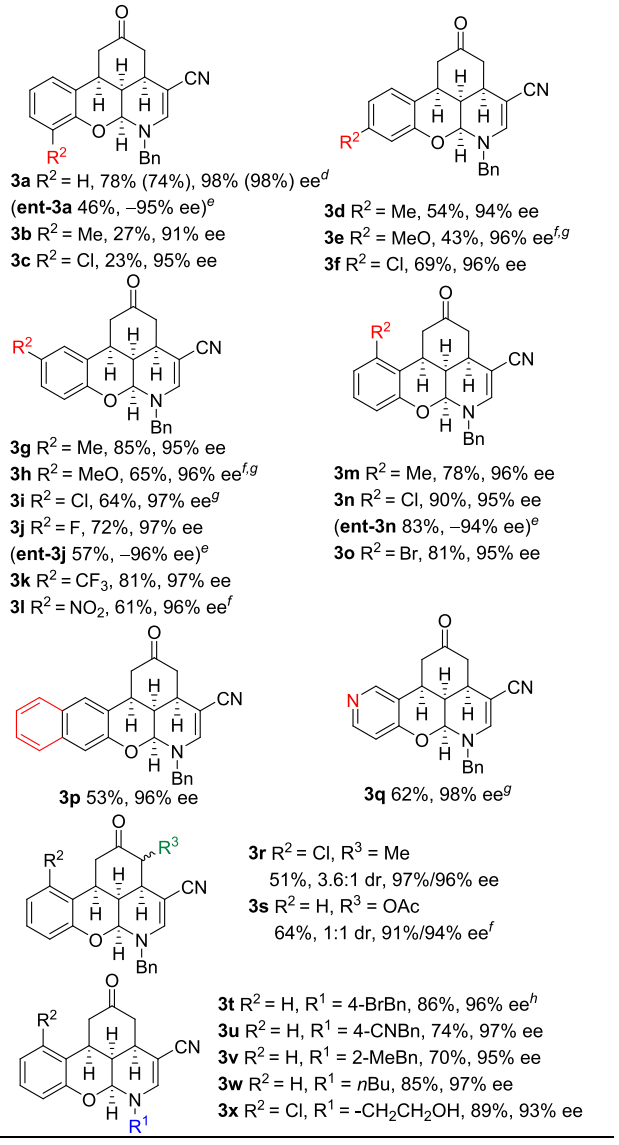
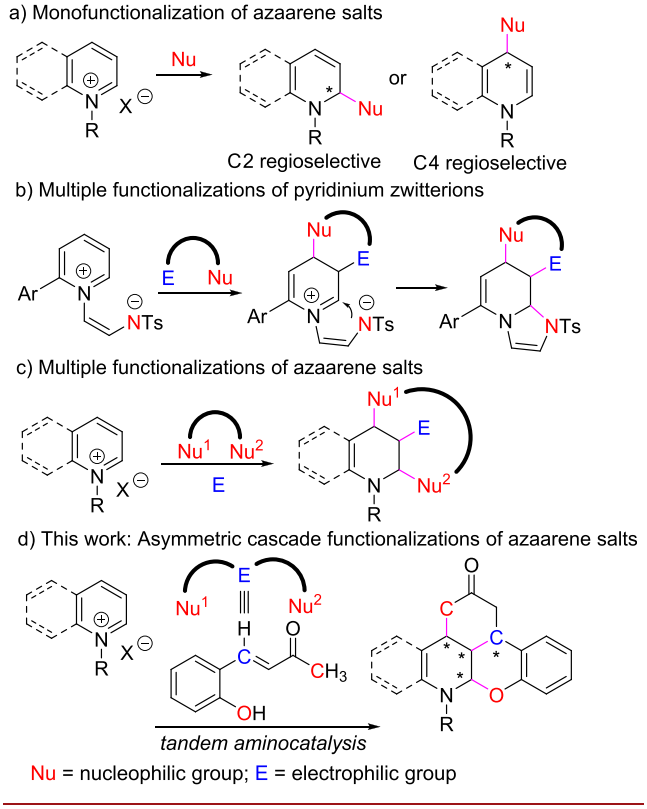
**Table 1. Substrate Scope of Multiple Functionalizations of Pyridinium Salts 1 with *o*-Hydroxybenzylideneacetones 2**[a,b,c]




[a]Unless noted otherwise, reactions were performed with **1a** (0.11 mmol, 1.1 equiv), **2** (0.1 mmol, 1.0 equiv), **C1** (20 mol %), **A1** (20 mol %), and **B1** (1.1 equiv) in DCM (1.0 mL) at rt for 24–96 h. [b]Yields of the isolated products are shown. [c]The ee values were determined by HPLC analysis on a chiral stationary phase. [d]Data in parentheses were obtained on a 1.0 mmol scale. [e]Data in parentheses were obtained with **C2**. [f]In DCM (2.0 mL). [g]At 4 °C for 60–192 h. [h]The absolute configuration of enantiopure **3t** was determined by X-ray analysis. The configurations of the other products were assigned by analogy.

**Scheme 1. Diverse Dearomative Modes of Pyridinium and Quinolinium Salts**




C3 showed lower reactivity with salt **1a** (products **3b** and **3c**), probably for steric reasons, whereas excellent enantioselectivity was still obtained. In addition, moderate to high yields along with outstanding levels of enantioselectivity were generally attained for enones **2** with different substituents at C4, C5, or even C6 (products **3d–o**). Naphthalene- and pyridine-based substrates also afforded similar good results (products **3p** and **3q**). Nevertheless, low diastereoselectivity was observed for enones **2** having a substituent at the $\alpha'$-position, but the enantiocontrol was still excellent for both isomers (products **3r** and **3s**). On the other hand, pyridinium salts **1** with diverse *N*-benzyl or other *N*-alkyl substituents were well-tolerated in the reactions with enone **2a** (products **3t–x**). Moreover, when amine **C2** from quinidine was employed, the corresponding products with the opposite configuration were produced with similar good data (Table 1, data in parentheses). It should be noted that the use of pyridinium salts with a 3-cyano group was important for the cascade reaction, and messy or inert reactions were observed for the salts with other types of functionalities.[10]

Encouraged by the above results, we further attempted to extend this strategy to multiple functionalizations of quinolinium salts. Although trace product (<5%) was observed when a simple *N*-benzylquinolinium salt was used, substrate **4a** with a 6-nitro group showed promising reactivity with enone **2a** under the previous catalytic conditions, delivering the fused product **5a** (Table 2) effectively but with poor enantiocontrol (>19:1 dr, 3% ee). To enhance the enantioselectivity, a number of amine catalysts and additives were investigated.[10] Gratifyingly, under the catalysis of a newly designed amine **C3** condensed from quinine and L-*tert*-leucine in combination with racemic mandelic acid (**A2**) and $Na_2HPO_4$, the model reaction proceeded smoothly


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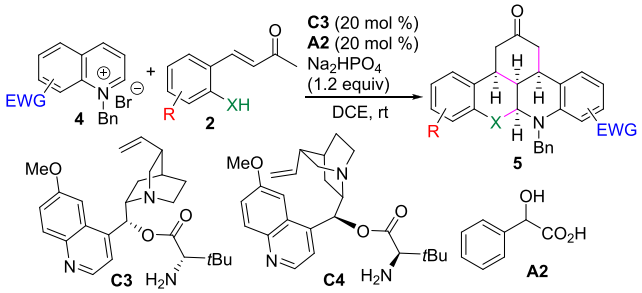
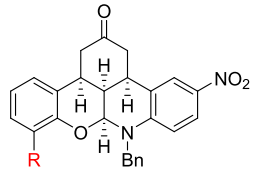
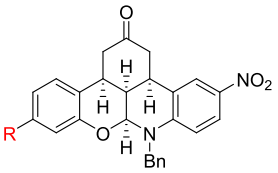
**Table 2. Substrate Scope of Multiple Functionalizations of Quinolinium Salts 4**[a,b,c]

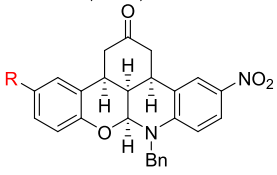


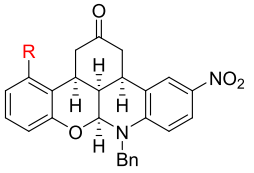

**5a** R = H, 70%, 89% ee
(**ent-5a** 66%, –89% ee)[d]
**5b** R = Me, 67%, 84% ee[e]
**5c** R = Cl, 58%, 81% ee



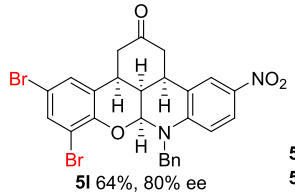

**5d** R = Me, 66%, 86% ee
**5e** R = Cl, 55%, 83% ee[e]
(**ent-5e** 67%, –88% ee)[d]



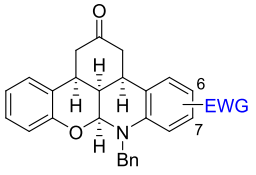

**5f** R = Me, 78%, 86% ee
**5g** R = MeO, 73%, 88% ee
**5h** R = F, 73%, 87% ee
**5i** R = Cl, 83%, 89% ee
(**ent-5i** 82%, –86% ee)[d]



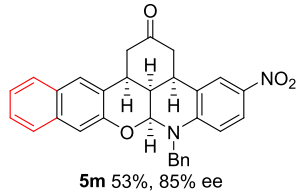

**5j** R = Me, 57%, 81% ee
**5k** R = Cl, 44%, 80% ee[f]



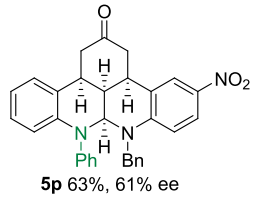

**5l** 64%, 80% ee




**5n** EWG = 6-CN, 77%, 82% ee
**5o** EWG = 7-$NO_2$, 62%, 89% ee




**5m** 53%, 85% ee

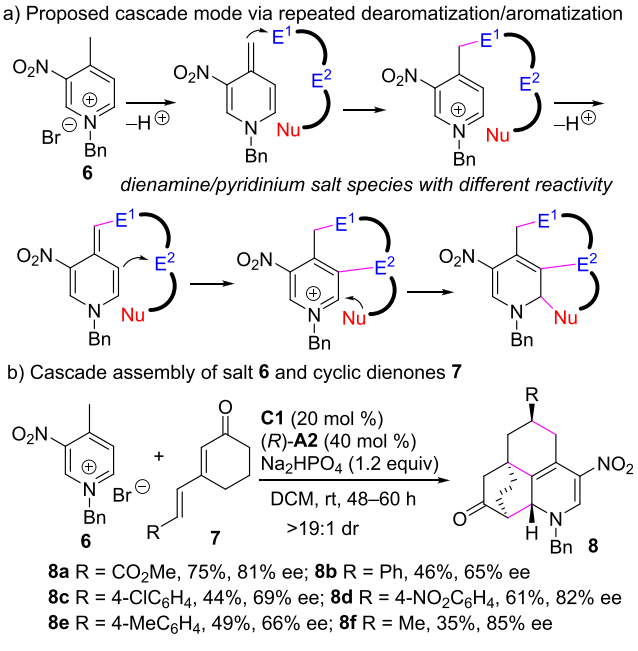



**5p** 63%, 61% ee

[a]Unless noted otherwise, reactions were performed using **4** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol, 1.0 equiv), **C3** (20 mol %), **A2** (20 mol %), and $Na_2HPO_4$ (0.1 mmol, 1.2 equiv) in DCE (2.0 mL) at rt for 48–60 h. [b]Yields of the isolated products are shown. [c]The ee values were determined by HPLC analysis on a chiral stationary phase. [d]Data in parentheses were obtained with **C4**. [e]In DCE (1.0 mL). [f]The absolute configuration of enantiopure **5k** was determined by X-ray analysis. The configurations of the other products were assigned by analogy.

in 1,2-dichloroethane (DCE) at room temperature, and product **5a** was obtained in 70% yield with good enantiocontrol (89% ee) (Table 2). Consequently, an array of enones **2** were explored in the reactions with quinolinium salt **4a**. As summarized in Table 2, in general, the series of trifunctionalized products **5b–m** were furnished in moderate yields with good enantioselectivities. In addition, quinolinium salts **4** with a 6-cyano or 7-nitro group also exhibited good reactivity under the same catalytic conditions

**Scheme 2. Cascade Assembly of Pyridinium Salt 6 with Cyclic Dienones 7**




**8a** R = $CO_2Me$, 75%, 81% ee; **8b** R = Ph, 46%, 65% ee
**8c** R = 4-$ClC_6H_4$, 44%, 69% ee; **8d** R = 4-$NO_2C_6H_4$, 61%, 82% ee
**8e** R = 4-$MeC_6H_4$, 49%, 66% ee; **8f** R = Me, 35%, 85% ee

(products **5n** and **5o**). Moreover, it was pleasing that an *o*-amino enone was applicable, although the product **5p** was attained in modest yield and enantioselectivity. We also tested the reactions with amine **C4** condensed from quinidine and D-*tert*-leucine, and the desired products with the opposite enantiopurity were provided with similar good ee values (Table 2, data in parentheses).

We recently reported that *N*-benzyl-4-methylpyridinium salt **6** could form a dearomative dienamine-type intermediate after deprotonation, which was combined with benzylideneacetones to give spirocycles via iminium ion catalysis.[12] We further envisaged that salt **6** would potentially perform as a multireactive agent, as proposed in Scheme 2a, through a repetitive dearomatization/aromatization process. To our gratification, cyclic dienone[13] **7a** (R = $CO_2Me$) could be utilized as a suitable partner under the catalysis of amine **C1** and acid (*R*)-**A2**,[10] efficiently furnishing the fused and bridged architecture **8a** in moderate yield with good enantioselectivity via a domino regioselective Michael/Michael/Mannich sequence. Other cyclic dienones **7** bearing a *δ*-aryl or -methyl group generally showed lower reactivity, and the desired frameworks **8b–f** were produced in fair yields with moderate to good levels of enantiocontrol (Scheme 2b).[10]

As illustrated in Scheme 3, a one-pot Friedländer quinoline synthesis was readily realized to afford the complex architecture **10** from product **3a** and 2-aminobenzaldehyde (**9**). Interestingly, an *N*-debenzylative aromatization process along with the reduction of nitro group was observed to give product **11** from the bridged skeleton **8a** under simple Pd/C-catalyzed hydrogenation conditions, albeit in a fair yield.[14]

In conclusion, we have demonstrated that activated pyridinium and quinolinium salts can be utilized in the asymmetric dearomative multiple functionalization reaction with *o*-hydroxybenzylideneacetones under the catalysis of cinchona-derived primary amines through dearomative addition and consecutive trapping of the reactive enamine intermediates and aminal formation. An array of fused heterocyclic architectures showing high molecular and stereogenic complexity were effectively constructed with good to excellent levels of enantioselectivity.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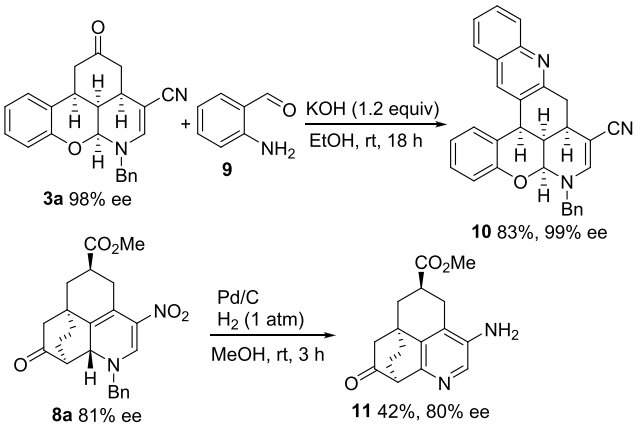
**Scheme 3. Synthetic Transformations of the Products**




Moreover, we also realized multiple functionalizations of 4-methylpyridinium salts with cyclic 2,4-dienone substrates through an unusual and repetitive dearomatization and aromatization activation process, finally affording bridged and fused frameworks with moderate to good enantiocontrol. We believe that the current dearomative multiple functionalization strategy may arouse interest in developing more asymmetric reactions to produce chiral heterocycles with high value in organic and medicinal chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02828.

Complete experimental procedures and characterization of new products; NMR and HRMS spectra and HPLC chromatograms (PDF)

### Accession Codes

CCDC 2022384−2022386 and 2023072 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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