Regio- and diastereoselective dearomatizations of N-alkyl activated azaarenes: the maximization of the reactive sites†

Hong-Jie Miao, Le-Le Wang, Hua-Bin Han, Yong-De Zhao, Qi-Lin Wang and Zhan-Wei Bu

An unprecedented base-promoted multi-component one-pot dearomatization of N-alkyl activated azaarenes was developed, which enabled the synthesis of complex and diverse bridged cyclic polycycles with multiple stereocenters in a highly regio- and diastereoselective manner. Besides, we realized the step-controlled dearomative bi- and trifunctionalization of quinolinium salts. These transformations not only achieved the maximization of the reaction sites of pyridinium, quinolinium and isoquinolinium salts to enhance structural complexity and diversity, but also opened up a new reaction mode of these N-activated azaarenes. A unique feature of this strategy is the use of easily accessible and bench-stable N-alkyl activated azaarenes to provide maximum reactive sites for dearomative cascade cyclizations. In addition, the salient characteristics including high synthetic efficiency, short reaction time, mild conditions and simple operation made this strategy particularly attractive.

Introduction

The dearomatization reaction has emerged as an expedient and versatile synthetic strategy to construct three-dimensional complex molecular skeletons from easily available flat aromatic compounds. Within this realm, significant attention has been directed toward the dearomatization of arenes and heteroarenes to assemble cyclic and heterocyclic compounds. Despite the high synthetic value of this strategy, the inherent challenge lies in the low reactivity of the aromatic substrates due to their reluctance to lose aromaticity as well as the difficulty in controlling the regio- and stereoselectivity in the course of generating the target three-dimensional products. In view of the salient features of pyridine, quinoline and isquinoline including ready availability, stability and ease of handling, the dearomatization of these \( \text{N} \)-activated azaarenes, where the C-2 and C-4 positions are active sites, represents one of the most efficient and robust approaches for the synthesis of hydrogenated azaarenes, which are common molecular architectures of a number of biologically active natural products and pharmaceuticals.\(^a\)

A survey of literature revealed that the reaction modes of pyridinium, quinolinium and isoquinolinium salts were mainly divided into two categories (Scheme 1a). The first one was the extensively studied monofunctionalization of pyridinium,\(^3\) quinolinium\(^4\) and isoquinolinium salts\(^5\) by taking advantage of their electrophilic activity via nucleophilic attack at the more electron-deficient carbons. However, for pyridinium and quinolinium salts, both the C-2 and C-4 positions are active sites. Thus, the regioselectivity of these additions was a main issue of concern. Generally, mixtures of regioisomers were observed in many cases. Introduction of an electron-withdrawing group at the C-3 position could regioselectively favor the C-4 nucleophilic attack.\(^6\) The second one was the sparsely reported bifunctionalization of these \( \text{N} \)-activated azaarenes, where the C-2 and C-4 positions of pyridinium and quinolinium salts and the C-1 and C-3 positions of isoquinolinium salts were skillfully employed to construct interesting bridged cyclic azaheterocycles (Scheme 1b).\(^7\) Although these elegant strategies have proved to be quite successful to assemble hydrogenated azaarenes via dearomative nucleophilic additions, only one or two reactive sites were exploited, which largely restricted their application for the construction of complex compounds. Therefore, it is highly important, but an extremely challenging task, to develop new reaction systems that facilitate the exploitation of all of the potential reactive sites of pyridinium, quinolinium and isoquinolinium salts to achieve structural complexity and diversity. Theoretically, pyridinium salts possess three electrophilic sites at the C-2, C-4 and C-6 positions and two nucleophilic sites at the C-3 and C-5 positions once the first attack by a nucleophile at the C-4 position was initiated (Scheme 2a). Similarly,
quino- linium and isoquinolinium salts also own two electrophilic sites and one nucleophilic site, respectively. Based on this knowledge, we envisioned that the maximization of the reactive sites of \( \text{N-alkyl activated azaarenes} \) could be achieved to enable the construction of complex and diverse bridged cyclic heterocycles by choosing the appropriate binucleophile and electrophile via a one-pot three-component dearomative cascade reaction (Scheme 2b). Actually, \( \text{N-alkyl activated azaarenes} \) themselves could be capable of behaving as electrophiles.

In this scenario, there were three inherent synthetic challenges: (1) the dearomative multifunctionalization of pyridinium, quino- linium and isoquinolinium salts has never been studied; (2) the appropriate binucleophile and suitable reaction conditions had to be found to improve the synthetic efficiency and control the regioselectivity and stereoselectivity; (3) the generation of multiple stereocenters embedded into bridged ring systems was a big challenge. As a continuation of our program aiming at the exploration of new cascade reactions for the construction of bridged rings with high synthetic efficiency and excellent stereocontrol,\(^8\) herein, we wish to present a base-promoted diastereoselective one-pot multicomponent dearomative cascade reaction of pyridinium, quino- linium and isoquinolinium salts, which realized the maximization of the active reactive sites of these \( \text{N-alkyl activated azaarenes} \) for dearomatization to construct diverse and complex bridged ring systems with multiple stereocenters. Such skeletons are privileged structural units of numerous natural products and biologically active pharmaceuticals.\(^9\)

### Results and discussion

As an initial study, enaminone 1a and \( \text{N-benzyl-3-nitropyridinium salt 2a} \) were chosen as the model substrates to test the feasibility of our synthetic design. When the reaction was conducted in \( \text{CH}_2\text{CN} \) at \( 60 \, ^\circ \text{C} \) with 2.0 equivalents of \( \text{Cs}_2\text{CO}_3 \) as the base, gratifyingly, the desired bridged polycycle product 3a was delivered in 12\% yield with complete regio- and diastereomeric control, whose structure was unambiguously verified by a comprehensive NMR, HRMS and X-ray analysis (Table 1, entry 1). This preliminary result definitely indicated that the dearomative cascade annulation of pyridinium salts was feasible. The formation of 3a was very appealing from the perspective of the reaction process and product structure. This transformation opened up an unprecedented reaction mode of pyridinium salt, where all of the five active sites were tactfully utilized to simultaneously construct five new bonds, two bridged rings as well as a challenging fused cyclobutane and eight stereocenters in a highly regio- and diastereoselective one-pot fashion. Moreover, the product contained some useful functional groups, such as nitro, carbonyl and a cyclic enamine, which offered versatile platforms for further architectural modifications.

To improve the synthetic efficiency, some inorganic and organic bases were evaluated. Among them, 1,1,3,3-tetramethylguanidine (TMG) was identified to be optimal in terms of yield and reaction time, in which the reaction went to full conversion within 5 min, affording 3a in 87\% yield (Table 1, entry 8). Remarkably, in this condition, the product was precipitated from the homogenous reaction mixture. So only a filtration process was needed to purify it, which largely simplified the purification procedure and met the requirement of green chemistry. Then, the reaction media were examined and the results suggested that they all gave inferior yields compared with \( \text{CH}_2\text{CN} \) (Table 1, entries 9–11 vs. 8). Finally, the loadings of N-benzyl-3-nitropyridinium salt 2a were investigated. When 2.2 equivalents of 2a were used, product 3a was precipitated out in a yield of 95\%. No increment in yield was observed on further raising the amount of 3a to 2.4 equivalents.

To achieve the asymmetric synthesis of 3a, we also examined some chiral bases, including cinchona alkaloids and their...
derivatives and chiral guanidine (for details, see Table S1 on page S19 of the ESI†). However, the results with respect to yields and enantioselectivity were quite disappointing. Consequently, the optimal conditions for the formation of complex bridged cyclic polycycle 3a were identified to be: 0.15 mmol of 1a with 2.0 equivalents of TMG in the presence of 2.0 equivalents of base in 0.8 mL of specified solvent at 60 °C.† Isolated yields obtained by column chromatography. † Isolated yields obtained by filtration of the precipitate. ‡ 2.2 equivalents of 2a were used. †‡ 2.4 equivalents of 2a were used. DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMG = 1,1,3,3-tetramethylguanidine.

With the optimized reaction conditions in hand, the substrate scope with respect to different enamines 1 was first explored and the results are highlighted in Scheme 3. These transformations had a wide tolerance of arylation-derived enamines with different substitution patterns and electron properties, affording the corresponding products 3a–p in 51–97% yields within 5 minutes. Notably, when R1 was located at the ortho-position of arylation, new kinds of atropisomers 3m–p were delivered in 51–88% yields, albeit with low diastereoselectivities. This promising finding not only provides a robust and facile method to access new atropisomers, but also represents a valuable complement to the existing appealing protocols. Other than arylation-derived enamines, aliphatic amine-derived ones were also compatible, affording 3q–s in 24–41% yields with complete diastereomeric control. Particularly, furfuryl amine-derived enaminoine also turned out to be a suitable reaction partner. Besides, acetylaceton and ethyl benzoylecetate derived acyclic enamiones could participate in this reaction successfully, thus facilitating the synthesis of 3u and 3v in 42% and 43% yields, respectively. An evaluation of the substituent effect of R2 on 3-nitropyridinium salts 2 revealed that not only were the methyl and ethyl groups accommodated well in this dearomative cascade cyclization, more hindered allyl, n-propyl and n-butyl groups were also amenable, enabling the construction of 3w–2a in good to excellent yields with complete diastereomeric control.

Later on, we investigated the effect of the substituents on the C3-position of pyridinium salts (Scheme 4). In sharp contrast to 3-nitropyridinium salt 2a, replacement of the nitro group with cyano and trifluoromethyl resulted in different reactivities, in which only bifunctionalization occurred for 2g and 2h by regioselective attack at C-2 and C-6 positions, affording bridged polycyclic N,N-ketals 3za and 3zc in 50% and 41% yields, respectively.

After successfully maximizing the active sites of pyridinium salts by the dearomative cascade strategy, we further extend this reaction system to quinolinium salts. With the first attempt of the reaction between enaminoine 1a and N-benzyl quinolinium salt 4a in CH3CN at 60 °C, the trifunctionalized dearomatization product 5a, featured by an interesting fusion of bioactive bridged N,O-ketal and 1,2-dihydroquinoline, was precipitated out from the reaction mixture, and was obtained in 98% yield in a highly diastereoselective manner (Scheme 5). Although the product 5a contained four contiguous tertiary stereocenters including two bridgehead stereocenters, only one diastereoisomer was obtained. After flash silica gel column chromatography, 5a was partially decomposed into bifunctionalized product 6a through a ring-opening/closure sequence. This result indicated that 5a was not very stable and it might be sensitive to acid. So, we conducted a one-pot two-step reaction of 1a and 4a. After the first TMG-promoted three-component dearmomatization trifunctionalization went to completion, one

### Table 1 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs2CO3</td>
<td>CH3CN</td>
<td>58 h</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>K2CO3</td>
<td>CH3CN</td>
<td>18 h</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Na2CO3</td>
<td>CH3CN</td>
<td>18 h</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>CH3CN</td>
<td>18 h</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>TMG</td>
<td>CH3CN</td>
<td>27 h</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>DBU</td>
<td>CH3CN</td>
<td>33 h</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>NEt3</td>
<td>CH3CN</td>
<td>3 h</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>TMG</td>
<td>CH3CN</td>
<td>5 min</td>
<td>87†</td>
</tr>
<tr>
<td>9</td>
<td>TMG</td>
<td>CHCl3</td>
<td>4 h</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>TMG</td>
<td>Toluene</td>
<td>4 h</td>
<td>74‡</td>
</tr>
<tr>
<td>11</td>
<td>TMG</td>
<td>EtOAc</td>
<td>20 min</td>
<td>58</td>
</tr>
<tr>
<td>12‡</td>
<td>TMG</td>
<td>CH3CN</td>
<td>5 min</td>
<td>95‡</td>
</tr>
<tr>
<td>13‡</td>
<td>TMG</td>
<td>CH3CN</td>
<td>5 min</td>
<td>80‡</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, the reactions were conducted with 0.15 mmol 1a with 2.0 equivalents of 2a in the presence of 2.0 equivalents of base in 0.8 mL of specified solvent at 60 °C.† Isolated yields obtained by column chromatography. † Isolated yields obtained by filtration of the precipitate. ‡ 2.2 equivalents of 2a were used. †‡ 2.4 equivalents of 2a were used. DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMG = 1,1,3,3-tetramethylguanidine.
equivalent of trifluoroacetic acid was added to the reaction mixture, and the desired bifunctionalized bridged $N,N$-ketal product 6a was generated smoothly in 99% yield with excellent diastereoselectivity.

This appealing step-controlled diverse synthesis prompted us to further investigate the substrate scope for the diastereoselective dearomative bi- and trifunctionalization of quinolinium salts. As demonstrated in Scheme 6, all of the reactions went to full conversion within 5 minutes to afford a series of trifunctionalized products 5a–s in 61–99% yields. Moreover, the workup procedure was extremely simple. All of the products were precipitated out from the reaction mixture and only an easy filtration process was needed to purify them. These prominent merits including high synthetic efficiency, short reaction time and simple operation make this transformation very attractive.

When phenanthrolinium salt 4k and 3-methyl quinolinium salt 4j were used as substrates, only dearomative bifunctionalizations took place to afford 7 and 8 in 87% and 51% yields, respectively (Scheme 7). Next, we turned our attention to the one-pot two-step dearomative bifunctionalization of quinolinium salts. As summarized in Scheme 8, both enamines 1 and quinolinium salts 4, irrespective of their substitution patterns and electron character, were tolerable, and participated in these transformations efficiently in a highly diastereomeric fashion, thus furnishing the corresponding products 6a–t in 79–99% yields.

Finally, we moved on to examine the reactivity of isoquinolinium salt 9a. Likewise, the highly regio- and diastereomeric trifunctionalized product 10a was generated in 36% yield when 2.0 equivalents of TMG were used as the base (Table S2,† entry 1). To benefit the yield, we investigated the effect of various bases and their loadings (for detailed condition optimization, see Table S2† on the page S48 of the ESI†), and we identified that 3.6 equivalents of DBU were the best of choice. Subsequently, the substrate scope was explored by using a variety of enamines 1 and isoquinolinium salts 9 (Scheme 9). Gratifyingly, all of them could participate in this transformation successfully to afford 10a–o in 82–97% yields. Remarkably, use of ortho-fluoro-substituted aniline-derived enamine as the substrate led to the synthesis of atropisomer 10l in 90% yield with 1.6 : 1 dr. When 4-bromoisoquinolinium salt 9d was employed, the highly diastereoselective bifunctionalization occurred instead of the trifunctionalization to deliver 10p as a single diastereomer in 54% yield (Scheme 10). The difference in reactivities of 9d and 9a–c may be caused by the steric hindrance, which disfavored the subsequent addition with another isoquinolinium salt.

To demonstrate the synthetic robustness, a preparative-scale experiment was conducted with 2.0 mmol of enamine 1d and
4.4 mmol of \(N\)-benzyl-3-nitropyridinium salt \(2a\) (Scheme 11). Delightfully, the reaction proceeded smoothly to give \(3d\) in diminished but acceptable yield within 5 minutes (0.89 g, 69% yield), thus suggesting that this protocol has the potential for scale-up preparation.

To further highlight the synthetic applicability, some chemical transformations of \(3g\) were carried out (Scheme 12). By subjecting \(3g\) to the NaBH\(_4\)–NiCl\(_2\) reductive system, the two nitro groups in \(3g\) were reduced into hydroxylamine and oxime respectively, accompanied by four-membered all-carbon ring opening. This transformation went to completion within 10 min with the formation of the corresponding functionalized product \(11\) in 62% yield with a ratio of 10 : 1 Z/E. In addition, the presence of a bromine atom in \(3g\) offers a convenient platform for further elaboration to generate molecules with more diverse and complex structures. Thus, two palladium-catalyzed Suzuki couplings of \(3g\) with 4-chlorophenyl boronic acid and 2-indolyl boronic acid were performed, which afforded \(12\) and \(13\) in 99% and 73% yields, respectively.

The structures and the relative configurations of \(3a, 3zb, 5m, 6n, 10g, 10p\) and \(11\) were unequivocally verified by X-ray analysis.\(^{12}\) The relative configurations of other products \(3, 5, 6\) and \(10\) were assigned by analogy.

Based on the experimental results, plausible mechanisms were proposed to rationalize the reaction pathways. As shown in...
A unique feature of this strategy is the use of easily accessible and bench-stable N-alkyl activated azaarenes, which may largely benefit the prospective reaction designs. A unique feature of this strategy is the use of easily accessible and bench-stable N-alkyl activated azaarenes to provide maximum reactive sites for dearomative multi-component one-pot cascade cyclizations. In addition, the salient characteristics including high synthetic efficiency, short reaction time, mild conditions and simple operation made this strategy particularly attractive. We expect that this fascinating strategy will stimulate the design of new related reactions for the facile construction of natural products and biologically interesting compounds.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


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