Stereoselective Synthesis of Benzo[a]quinolizidines via Aerobic DDQ-Catalyzed Allylation and Reductive Cyclization

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ABSTRACT: Stereoselective synthesis of C4-substituted benzo[a]-quinolizidines via redox-controlled catalytic C–C-bond-forming reactions was carried out. Aerobic DDQ-catalyzed allylation of N-Cbz tetrahydroisoquinolines efficiently provided α-allylated products 5, which were transformed to enones 6 via cross-metathesis reactions using the second-generation Hoveyda–Grubbs catalyst. Palladium-catalyzed hydrogenation of 6 prompted alkene reduction, protecting group removal, and intramolecular reductive amination in one step to afford the desired benzo[a]quinolizidines 7 as single diastereomers.

INTRODUCTION

Benzo[a]quinolizidine, a common structural motif present in alkaloids, is found in various biologically active natural products and pharmacologically useful chemical probes.1,2 For example, protoemetinol is proposed to be a crucial intermediate in the biosynthesis of biologically active alkaloids such as cephaeline and emetine (Figure 1).3 Emetine, an antiprotozoal agent, inhibits ribosomal protein synthesis in eukaryotic cells and is often used for protein degradation studies.4 Tetrabenazine has been reported as a reversible inhibitor of VMAT2 (vesicular monoamine transporter 2), clinically used for the symptomatic treatment of motor neuron dysfunction associated with Huntington’s disease.5,6

Owing to the biological importance of the benzo[a]-quinolizidine ring system, several synthetic approaches have been reported using different cyclization processes. These include the Pictet–Spengler reaction, the Bischler–Napieralski reaction, ring-closing metathesis, the aza-Diels–Alder reaction, Dieckmann condensation, and the intramolecular Heck reaction.7 Studies on novel synthetic methods toward benzoquinolizidines based on organocatalysis have recently been reported. Zhao group described a one-pot Vilsmeier–Haack/organocatalyzed Mannich reaction for the preparation of benzoquinolizidines.8 Jacobsen and co-workers demonstrated the effective synthesis of benzo[a]quinolizine-2-ones via aminourea-catalyzed formal aza-Diels–Alder reactions.9

We recently reported the synthesis of C4 or C3 substituted benzo[a]quinolizidines via aza-Michael addition of tetrahydroisoquinolines (THIQ) to alkyl vinyl ketones, followed by α-C-H oxidative Mannich cyclization.10 In this approach, DDQ was used as a major oxidant for generating an iminium intermediate, but a stoichiometric amount of reagent was required, making it difficult to eliminate the resulting 2,3-dichloro-5,6-dicyanohydroquinone (DDQH2).11 Now, by expanding our interests in the DDQ-catalyzed coupling reactions,6c,10,12 we have planned a new approach to synthesize benzoquinolizidines 7 using an oxidative allylation as the key reaction, which was originally developed by Lee and co-workers13a (Scheme 1). In this strategy, an allyl group will be substituted at the α-position of nitrogen in THIQ via DDQ catalyzed C–C bond formation.13 Although, several DDQ-catalyzed reactions using metal oxidants such as FeCl3,14 Mn(OAc)3,15 and MnO216 have been reported, we devised to exploit molecular oxygen as an ideal oxidant considering atomic efficiencies and metal-free conditions. Once the aerobic allylation is completed under the catalytic conditions, the cross-metathesis of 5 with vinyl ketones yields enone 6, which subsequently undergoes reductive cyclization to afford benzoquinolizidines 7. Using this approach, we expect the...
Scheme 1. Synthesis of Benzoquinolizidines via Oxidative C–C Bond Formation

- Previous work
  - Michael addition
  - Oxidative allylation
  - Cross metathesis
  - Reductive cyclization

- This work
  - Stoichiometric DDQ
  - Aerobic DDQ catalysis

Table 1. Optimization of Aerobic DDQ-Catalyzed Oxidative Allylation Reaction

| entry | acid (equiv) | temp (°C) | time (h) | yield (%) |
|-------|--------------|-----------|----------|-----------|
| 1     | AcOH (12)    | rt        | 24       | 15 (40)   |
| 2     | AcOH (12)    | 50        | 48       | 55        |
| 5     | AcOH (12)    | rt        | 24       | 72        |
| 4     | AcOH (12)    | rt        | 24       | 16        |
| 5     | TFA (3)      | rt        | 15       | 17        |
| 6     | TFA (5)      | rt        | 15       | 16        |
| 7     | TFA (7)      | rt        | 15       | 73        |
| 8     | TFA (7)      | 50        | 2        | 55        |
| 9     | TFA (7)      | rt        | 1        | 30        |
| 10    | TFA (7)      | rt        | 15       | 65        |
| 11    | -            | rt        | 15       |           |
| 12    | TFA (7)      | rt        | 24       |           |
| 13    | TFA (7)      | rt        | 15       | 52        |

"The required reaction time for the formation of Int-1 in step (i).
"Isolated yield. " Allytributylstannane (2.0 equiv) was used. " Yield based on the recovered starting material. " LiClO₄ (1.0 equiv) was added. " TBN (0.5 equiv) was used instead of NaN₃. " The reaction was performed under air. " The reaction was performed without acid. " The reaction was performed without NaN₃. " The reaction was performed in the absence of DDQ.

RESULTS AND DISCUSSION

Our initial study begins with the DDQ-catalyzed oxidative allylation of THIQ. In general, aerobic DDQ-catalyzed oxidation required cocatalysts such as AIBN, Fe(NO₃)₃, Laccases, and TBN because molecular oxygen itself cannot directly oxidize DDQH₂ to DDQ during the catalytic cycle. Considering the practical and environmental aspects of our study, we selected the DDQ/NaNO₂ catalytic system developed by Gao and co-workers for the oxidative allylation reactions. In this system, it has been reported that acid be used as a crucial additive to activate nitrite to nitrogen oxide. Meanwhile, we selected the benzyloxycarbonyl (Cbz) group as an N-protecting group of THIQ because of its easy removal under catalytic hydrogenation, and thus the corresponding amine could be directly applicable to one-pot reductive amination in the final stage. Thus, the allylation reactions of N-Cbz-protected THIQ 4a, in the presence of DDQ are optimized as demonstrated in Table 1.

As per the reported procedure, the allylation reaction of 4a was performed with DDQ (0.1 equiv), NaNO₂ (0.2 equiv), acetic acid (12.0 equiv), and allylstannane (5.0 equiv) under atmospheric oxygen pressure to afford 5a in 15% yield (entry 1). The low yield of 5a is presumably due to the low conversion of the starting material to acyliminium intermediate (40% based on recovered starting material). When the reaction proceeded at 50 °C, the yield was increased to 55% (entry 2). To improve the reactivity of acyliminium intermediate generated by DDQ oxidation, we used LiClO₄ (1.0 equiv) as a cation activator, which yields 72% of 5a (entry 3). When TBN was used as an alternative co-oxidant, the starting material was consumed, but 5a was obtained in only 16% yield (entry 4). On the other hand, trifluoroacetic acid (TFA) was also explored as an acid as it was assumed that it would activate NO and its conjugate base could improve the reactivity of acyliminium cation Int-1 as well. As the amount of TFA was increased, the yield was proportionally increased to 73% (entries 5–7). The reaction rate was also accelerated when an excess amount of TFA (7.0 equiv) was used (entry 7). Other reaction conditions such as high temperature and low allylstannane concentration led to lower yields of 5a (entries 8–9). The use of air as an oxygen source slightly reduced the yield to 65% (entry 10). Interestingly, we noticed that the reaction did not proceed without acid (entry 11) or NaNO₂ (entry 12), whereas the allylation occurred in the absence of DDQ to afford 5a in moderate yield but a longer reaction time was required (entry 13). The results indicate that the NO produced by treating NaNO₂ with TFA might activate the C–C bond reducing of internal alkene moiety, removal of N-protecting group, and reductive amination of the corresponding amine to occur in one-step to provide the desired target molecule 7. As it is challenging to access the tricyclic core in stereoselective fashion, this redox-controlled catalytic reaction would provide a facile pathway to synthesize the 2-substituted benzoquinolizidine ring system.

Herein, we report the stereoselective synthesis of benzoquinolizidines using three catalytic consecutive reactions, including aerobic DDQ-catalyzed allylation, cross-metathesis, and reductive cyclization.
H bond of THIQ at the α-position of nitrogen. A possible mechanism of the DDQ-catalyzed allylation under aerobic condition is proposed in Scheme 2. It has been reported that heteroatom-containing substrates can be oxidized by DDQ to generate oxocarbenium or iminium ion species through a hydride abstraction mechanism. Thus, hydride abstraction of THIQ 4 by DDQ in the presence of TFA forms iminium-trifluoroacetate complex Int-1, which undergoes allylation to afford the desired product 5. For catalytic cycle, molecular oxygen plays a critical role to form NO₂, which could oxidize DDQ₂ back to DDQ. In addition, the single electron transfer followed by hydrogen abstraction through a radical mechanism might not be ruled out because the reaction occurred without DDQ. Further investigations on the reaction mechanism are needed.

Using the optimized reaction conditions, we investigated the nature of substrate as shown in Scheme 3. The electron-rich substrates having methoxy group at 6- or 6,7-position afforded the corresponding allylated compounds 5b and 5c in high yields. Notably, small amount of TFA (5.0 equiv) was enough for the formation of acyliminium intermediate. Although, the allylation of electron-deficient THIQs required an extra amount of TFA (9.0 equiv) to yield the desired products 5d−5f in 84−85% yield. Under the same reaction conditions, 6-phenyl and 3,4-butoxy carbonyl substituted THIQs (5g and 5h) were obtained in 94 and 82% yields, respectively. N-Cbz-protected tetrahydro β-carbone proved to be an inefficient substrate, affording 5i only in 22% yield. The low yield is presumably due to nitrogen oxides-based side reactions such as nitration or nitrosation. Additionally, the sterically hindered methallylstannane and prenylstannane were well abided to produce the desired compounds 5j and 5k in good yields. Most of N-Cbz-protected THIQ 5 existed as rotamers, the structures of which were determined by analysis of the NMR experiment (see the compound characterization in the Supporting Information).

Next, we prepared a series of enones 6 via cross metathesis reactions as demonstrated in Scheme 4. Considering the reaction conditions, we found that the cross-metathesis reactions of 5 with methyl vinyl ketones (1.0 M in CH₂Cl₂) in the presence of a second-generation Hoveyda–Grubbs (HG2) catalyst at 45 °C afforded the desired enones 6a−i in good to excellent yields. The use of phenyl vinyl ketone or ethyl vinyl ketone as a substitute of methyl vinyl ketone also provided 6j and 6m in 84 and 81% yields, respectively. However, trisubstituted enone 6j and sterically hindered enone 6k were not obtained under different reaction conditions, such as using alternating catalysts, solvents, and temperatures. Additionally, enal 6n was synthesized through the cross-metathesis of 5b with 3,3-diethoxyprop-1-ene, followed by the acid-catalyzed hydrolysis of the corresponding acetal 6o.

The final product benzoquinolizidines 7 were synthesized via intramolecular reductive cyclization as shown in Scheme 5. The reaction conditions were examined using different solvent systems, concentrations, and amounts of palladium (Table S1). Indeed, the best yield (80%) of the desired benzoquinolizidine 7a was obtained when the catalytic hydrogenation of 6a with 15 wt % palladium (10% activated on charcoal) in methanol/CH₂Cl₂ (5:1, 0.04 M) under hydrogen (1 atm) at room temperature was performed. This optimal reaction condition was then applied to other substrates 6 to afford various substituted benzoquinolizidines 7 efficiently with excellent stereoselectivity. The compounds 6b and 6c with electro-donating groups were transformed into 7b and 7c in 91 and 63% yields, respectively. The halogen-substituted electron-deficient substrates 6d, 6e, and 6f were also cyclized to obtain the corresponding benzoquinolizidines, but unfavorable dehalogenation occurred in the case of 6e and 6f even when 5 wt % palladium was used. The 4,9-disubstituted tricyclic 7g, 4,6-disubstituted 7h, and carboline derivative 7i were produced in good yields as single diastereomers. Additionally, com-

Scheme 2. Proposed Mechanism of the DDQ-Catalyzed Allylation under Aerobic Conditions

Scheme 3. Variation of 5 in DDQ-Catalyzed Aerobic Oxidative Allylation

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Isolated yields. The yields in parentheses resulted from the reactions with AcOH instead of TFA. TFA (5.0 equiv) was used. TFA (9.0 equiv) was used. TFA (4.5 equiv) afforded only 63% yield. The stereochemistry was determined by the X-ray crystallographic analysis of the corresponding benzoquinolizidine 7h (vide infra).
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pounds 6l and 6m with different substituents at the R2 position (R2 = Ph or Et) gave the desired products 7l and 7m efficiently. Under the same reduction conditions, the aldehyde 6n was relatively tolerated to afford 7n in moderate yield.

The stereochemistry of the cyclized product 7 was confirmed by the NOE analysis of compound 7l. We observed a significant NOE enhancement between two protons at the C4 and C11b positions, which indicates that these protons have a cis-stereochemical relationship (see Figures S1 and S2). However, the comparison of 1H NMR spectra in all the compounds 7 revealed that the stereochemistry of compound 7h was different from other products. The single-crystal X-ray diffraction analysis of 7h revealed that the C11 angular proton is trans to both C4 and C6 protons (Figure 2). This stereochemical discrepancy was rationalized with the influence of the t-butyloxycarbonyl group in the THIQ ring on the C–C bond formation. The cis stereochemistry in most cases is presumably due to the hydrogen attack on the iminium intermediate Int-2 from the same side of the angular hydrogen. However, the t-butyloxycarbonyl group in Int-3 must be axially located at α'-position to nitrogen, avoiding the A1,3-strain. Thus, the allylation of Int-3 occurred at the face opposite to the ester group to afford 6h with trans 1,3-stereochemistry. Further reductive cyclization of 6h via the second iminium cation Int-4 to yield 7h could be controlled by the pseudoaxial ester group, in which the C4 and C6 protons are cis to each other.

### CONCLUSIONS

In this study, we developed a stereoselective synthesis of C4-substituted benzo[a]quinolizidines via three catalytic C–C bond forming consecutive reactions. First, the allylated THIQ 5 were prepared in high yield under an aerobic DDQ/NaNO2 catalytic system. Second, cross-metathesis reactions of 5 efficiently afforded a variety of enones 6a–m and enal 6n. Finally, palladium-catalyzed hydrogenation of 6 sequentially facilitated alkene reduction, Cbz-deprotection, and intramolecular reductive amination in one step to afford the desired tricycles 7 as single diastereomers. This novel and simple three-step protocol provides a catalytic and redox-controlled synthetic route to different benzo[a]quinolizidines. Further investigation on expanding the current aerobic DDQ catalytic system to synthesize other useful heterocycles is in progress in our laboratory.

### EXPERIMENTAL SECTION

**General Information.** All reactions were conducted using oven-dried glassware under an atmosphere of argon (Ar). All commercially available reagents and anhydrous solvents were obtained from Sigma-Aldrich, TCI, Alfa, Junsei, Samchun, DaeJung Chemical and were used without further purification. Solvents CH2Cl2 was dried and distilled following usual protocols. Organic solvents were evaporated with reduced
pressure using a rotary evaporator. Reactions were followed by TLC analysis using silica gel 60 F254 with fluorescent indicator using UV lamp and KMnO4 solution with heat as visualizing agents. Flash chromatography was carried out using Merck silica gel 60 (0.063–0.200 mm) and Kanto silica gel 60N (spherical, neutral). The 1H NMR spectra and 13C NMR spectra were measured with Bruker AVANCE III HD 400. 1H NMR chemical shifts are expressed in parts per million (δ) downfield to CHCl3 (δ = 7.26). 13C NMR chemical shifts are expressed in parts per million (δ) relative to the central CDCl3 resonance (δ = 77.0). Coupling constants in 1H NMR are in Hz. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. C7DCl3 was used as NMR solvent and standard material TMS (tetramethylsilane) was not contained.

**Representative Procedure for Allylation.** Benzyl 1-Allyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (5a). To a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (3.7 mg, 0.016 mmol) in CH2Cl2 (0.8 mL) was added TFA (88 μL, 1.1 mmol) at room temperature. The mixture was stirred for 5 min under air atmosphere. N-Cbz protected tetrahydroisoquinoline 4a (44 mg, 0.16 mmol) in CH2Cl2 (0.8 mL) and sodium nitrite (2.3 mg, 0.033 mmol) were added to the reaction mixture. The resulting solution was stirred at room temperature under O2 balloon for 1 h. After the starting material disappeared, allyltributylstannane (253 μL, 0.82 mmol) was added. After 30 min, the mixture was quenched with saturated aqueous NaHCO3 (15 mL) and extracted with CH2Cl2 (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford 5a (37 mg, 73%) as pale yellow oil. Rf = 0.46 (hexane/EtOAc = 5:1). 1H NMR (400 MHz, CDCl3, 1:1 mixture of carbamate rotamers seen at rt) δ 7.37–7.33 (m, 5H), 7.18–7.12 (m, 4H), 5.82 (m, 1H), 5.33–4.97 (m, 5H), 4.27 (m, 0.5H), 4.09 (m, 0.5H), 3.40 (m, 0.5H), 3.30 (m, 0.5H), 2.93 (m, 1H), 2.77 (d, J = 15.9 Hz, 1H), 2.61–2.54 (m, 2H). 13C NMR (100 MHz, CDCl3, rotamers seen) δ 155.5, 136.9, 136.7, 134.8, 134.7, 134.2, 134.0, 129.1, 128.7, 128.4, 128.1, 128.0, 127.9, 127.7, 127.2, 126.9, 126.7, 126.6, 126.1, 126.0, 117.5, 117.3, 67.2, 67.0, 54.4, 41.5, 41.2, 38.4, 37.7, 28.6, 28.4. HRMS (ESI) calcd for C29H32NO3 [M + H]+ 308.1645, found 308.1648.

**Representative Procedure for Cross-Metathesis.** Benzyl (E)-1-(4-Oxopent-2-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6a). A solution of N-Cbz-1-allyl-tetrahydroisoquinoline 5a (90 mg, 0.29 mmol) in CH2Cl2 (3 mL) and methyl vinyl ketone (71 μL, 0.88 mmol) were stirred at room temperature under an argon atmosphere. The solution was bubbling with argon for 10 min and then the second generation Hoveyda–Grubbs catalyst (13 mg, 0.020 mmol) was added at room temperature. The reaction mixture was stirred at 45 °C for 6 h and the solvent was removed under reduced pressure. The resulting crude oil was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:1) to afford 6a (81 mg, 80%) as brown oil. Rf = 0.51 (hexane/EtOAc = 1:1). 1H NMR (400 MHz, CDCl3, 1:1 mixture of carbamate rotamers seen at rt) δ 7.36–7.33 (m, 5H), 7.21–7.09 (m, 4H), 6.86–6.70 (m, 1H), 6.01 (d, J = 15.9 and 15.5 Hz, 1H), 5.42–5.26 (m, 1H), 5.21–5.07 (m, 2H), 4.27–4.05 (m, 1H), 3.38–3.33 (m, 1H), 3.01–2.87 (m, 1H), 2.79–2.70 (m, 3H), 2.16 and 2.07 (s, 3H), 13C NMR (100 MHz, CDCl3, rotamers seen) δ 198.7, 198.0, 155.5, 155.2, 144.4, 143.4, 136.7, 136.3, 136.1, 135.8, 134.2, 134.0, 133.5, 133.2, 129.3, 128.9, 128.6, 128.5, 128.2, 128.0, 127.7, 127.1, 127.0, 126.9, 126.7, 126.4, 126.3, 67.5, 67.2, 54.1, 53.9, 40.1, 38.5, 37.9, 28.6, 28.2, 26.9, 26.4. HRMS (ESI) m/z calcd for C32H38NNaO3 [M + Na]+ 372.1570, found 372.1573.

**Representative Procedure for Reductive Cyclization.** 4-Methyl-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinoline (7a). To a solution of benzyl (E)-1-(4-oxopent-2-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate 6a (51 mg, 0.15 mmol) in MeOH (3.0 mL)/CH2Cl2 (0.6 mL) was added Pd/C (10 wt %). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite with MeOH and diethyl ether, and the resulting solution was concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel (CH2Cl2/MeOH = 10:1) to afford 7a (23 mg, 80%) as yellowish oil.
Experimental details for synthesis of 5, 6, and 7; NOE experiments of 7H; X-ray crystallography data of 7H; reaction optimization; and all of the spectral data for new compounds (PDF)

Accession Codes
CCDC 2161939 contains 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, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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