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

Sunhwa Jung, Seungri Yoon, Jae Kyun Lee, and Sun-Joon Min*

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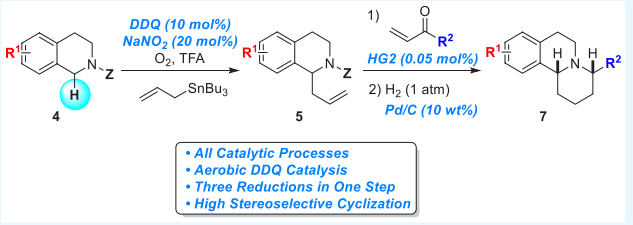
ABSTRACT: Stereoselective synthesis of C_4-substituted benzo[*a*]-quinolizidines via redox-controlled catalytic C−C-bond-forming reactions was carried out. Aerobic DDQ-catalyzed allylation of *N*-Cbz tetrahydroisoquinolines efficiently provided α-allylated products **5**, which were transformed to enones **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

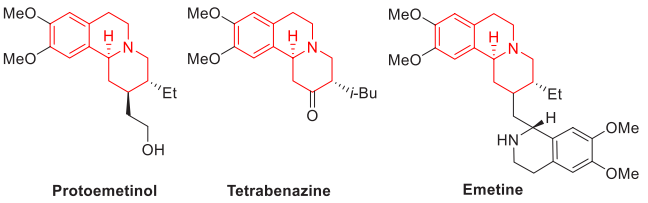


Figure 1. Representative benzo[*a*]quinolizidine derivatives.

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 C_1 or C_3 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 ($DDQH_2$).[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-workers[13a] (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 $FeCl_3$,[14] $Mn(OAc)_3$,[15] and MnO_2[16] 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

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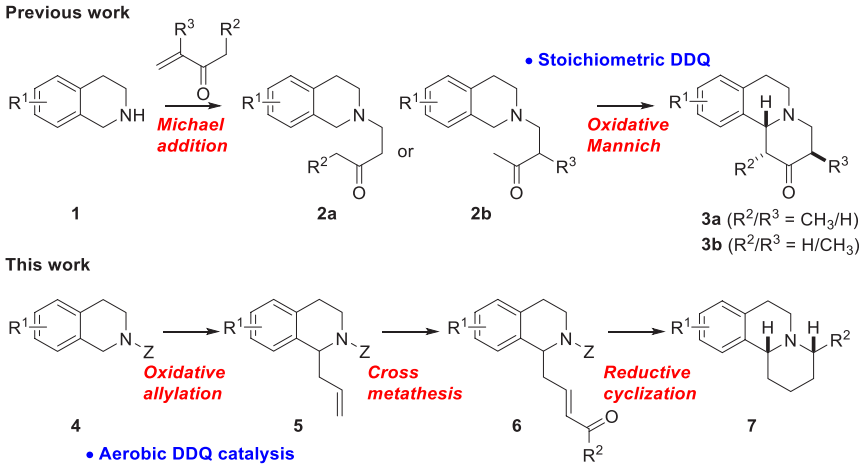
Scheme 1. Synthesis of Benzoquinolizidines via Oxidative C−C Bond Formation



reduction 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.

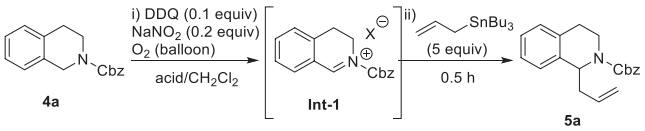
Herein, we report the stereoselective synthesis of benzoquinolizidines using three catalytic consecutive reactions, including aerobic DDQ-catalyzed allylation, cross-metathesis, and reductive cyclization.

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,[17] $Fe(NO_3)_3$,[18] Laccases,[19] and TBN[20] because molecular oxygen itself cannot directly oxidize $DDQH_2$ to DDQ during the catalytic cycle.[21] Considering the practical and environmental aspects of our study, we selected the DDQ/$NaNO_2$ catalytic system developed by Gao and co-workers[22] 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.[23] 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,[22] the allylation reaction of **4a** was performed with DDQ (0.1 equiv), $NaNO_2$ (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,[24] we used $LiClO_4$ (1.0 equiv) as a cation activator,[10] 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

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



entry	acid (equiv)	temp (°C)	time (h)[a]	yield (%)[b]
1[c]	AcOH (12)	rt	24	15 (40)[d]
2[c]	AcOH (12)	50	48	55
3[c,e]	AcOH (12)	rt	24	72
4[c,f]	AcOH (12)	rt	24	16
5	TFA (3)	rt	15	17
6	TFA (5)	rt	15	16
7	TFA (7)	rt	1	73
8	TFA (7)	50	2	55
9[c]	TFA (7)	rt	1	30
10[g]	TFA (7)	rt	15	65
11[h]	-	rt	15	
12[i]	TFA (7)	rt	24	
13[j]	TFA (7)	rt	15	52

[a]The required reaction time for the formation of **Int-1** in step (i). [b]Isolated yield. [c]Allyltributylstannane (2.0 equiv) was used. [d]Yield based on the recovered starting material. [e]$LiClO_4$ (1.0 equiv) was added. [f]TBN (0.5 equiv) was used instead of $NaNO_2$. [g]The reaction was performed under air. [h]The reaction was performed without acid. [i]The reaction was performed without $NaNO_2$. [j]The reaction was performed in the absence of DDQ.

also explored as an acid as it was assumed that it would activate $NaNO_2$ to NO and its conjugate base could improve the reactivity of acyliminium cation **Int-1** as well.[25] 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 $NaNO_2$ (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 $NaNO_2$ with TFA might activate the C−

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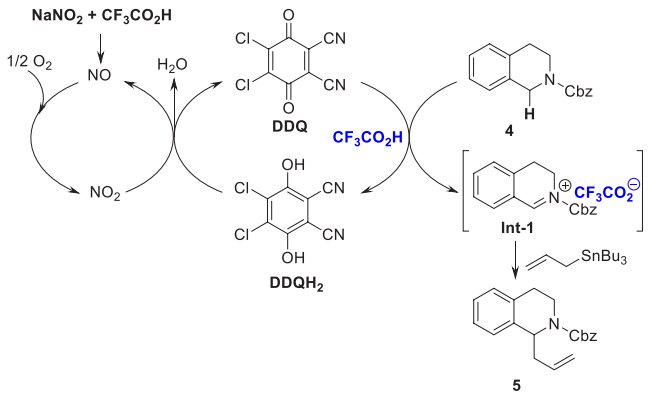
H bond of THIQ at the α-position of nitrogen.[26] A possible mechanism of the DDQ-catalyzed allylation under aerobic condition is proposed in Scheme 2. It has been reported that

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

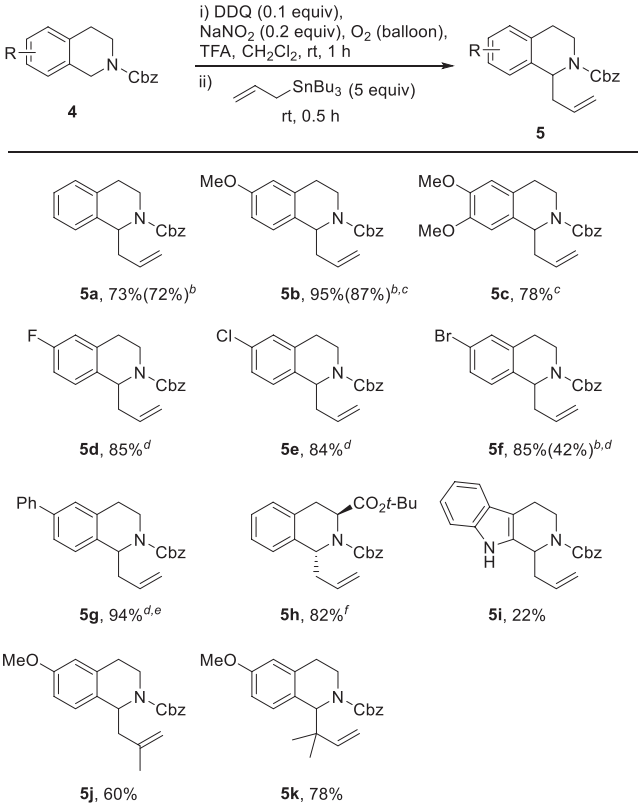


heteroatom-containing substrates can be oxidized by DDQ to generate oxocarbenium or iminium ion species through a hydride abstraction mechanism.[27] Thus, hydride abstraction of THIQ **4** by DDQ in the presence of TFA forms iminium-trifluoroacetate complex **Int-1**, which undergoes allylation to afford the desired product **5**. For catalytic cycle, molecular oxygen plays a critical role to form NO_2, which could oxidize $DDQH_2$ 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.[25] 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-*t*-butoxycarbonyl substituted THIQs (**5g** and **5h**) were obtained in 94 and 82% yields, respectively. *N*-Cbz-protected tetrahydro β-carboline 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 CH_2Cl_2) 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 **6l** and **6m** in 84 and 81% yields, respectively. However,

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



[a]Isolated yields. [b]The yields in parentheses resulted from the reactions with AcOH instead of TFA. [c]TFA (5.0 equiv) was used. [d]TFA (9.0 equiv) was used. [e]TFA (4.5 equiv) afforded only 63% yield. [f]The stereochemistry was determined by the X-ray crystallographic analysis of the corresponding benzoquinolizidine **7h** (*vide infra*).

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** was 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/CH_2Cl_2 (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-

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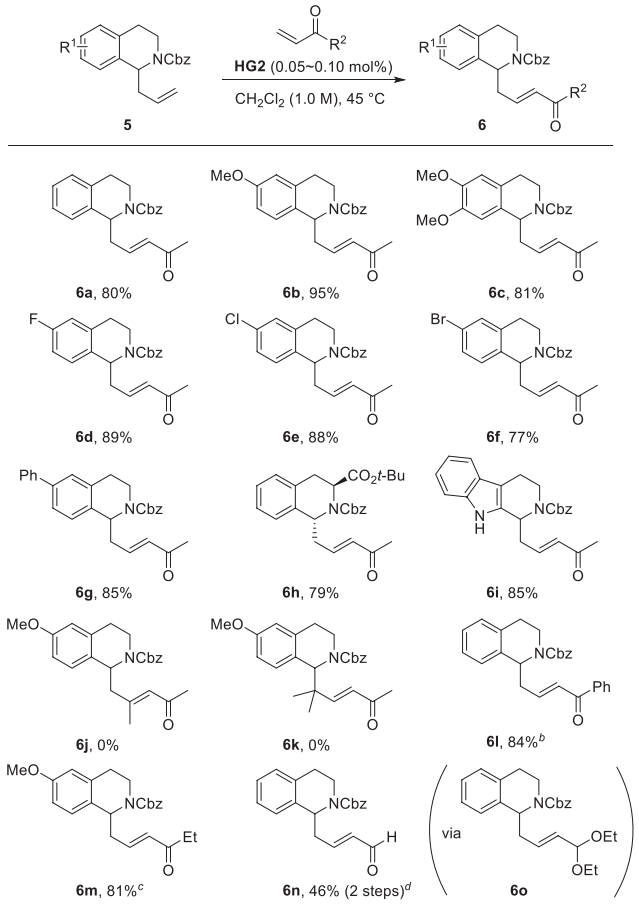
Scheme 4. Cross Metathesis Reactions of 5 with Vinyl Ketones[a]

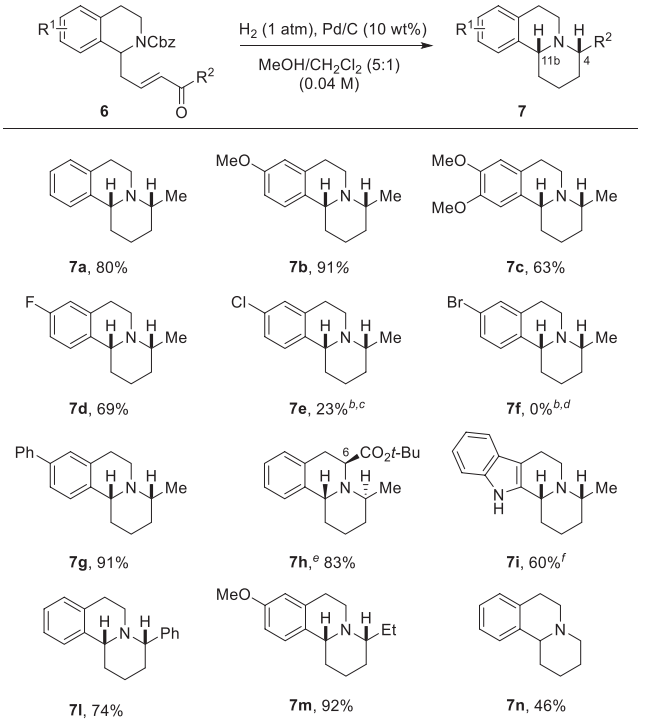


[a]Isolated yields. [b]Phenyl vinyl ketone was used. [c]Ethyl vinyl ketone was used. [d]The cross metathesis reaction of **5b** with 3,3-diethoxyprop-1-ene and subsequent hydrolysis of the corresponding product **6o** with formic acid were performed.

pounds **6l** and **6m** with different substituents at the R^2 position (R^2 = 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 C_4 and C_{11b} positions, which indicates that these protons have a *cis*-stereochemical relationship (see Figures S1 and S2). However, the comparison of ^{1}H 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 C_{11} angular proton is trans to both C_4 and C_6 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 $A^{1,3}$-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

Scheme 5. Reductive Cyclization of 6 Using Catalytic Hydrogenation[a]



[a]Isolated yields. [b]2.5 wt % of Pd/C (5 wt %) was used. [c]**7a** was obtained as a side product in 25% yield. [d]Only **7a** was obtained in 59% yield. [e]Optically active (all the compounds **7** were racemic except for **7h**). [f]Twenty-two wt % of Pd/C (10 wt %) was used. All the compounds **7** were racemic except for **7h**.

cation **Int-4** to yield **7h** could be controlled by the pseudoaxial ester group, in which the C_4 and C_6 protons are cis to each other.

CONCLUSIONS

In this study, we developed a stereoselective synthesis of C_4-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/$NaNO_2$ 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 provide 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 CH_2Cl_2 was dried and distilled following usual protocols. Organic solvents were evaporated with reduced

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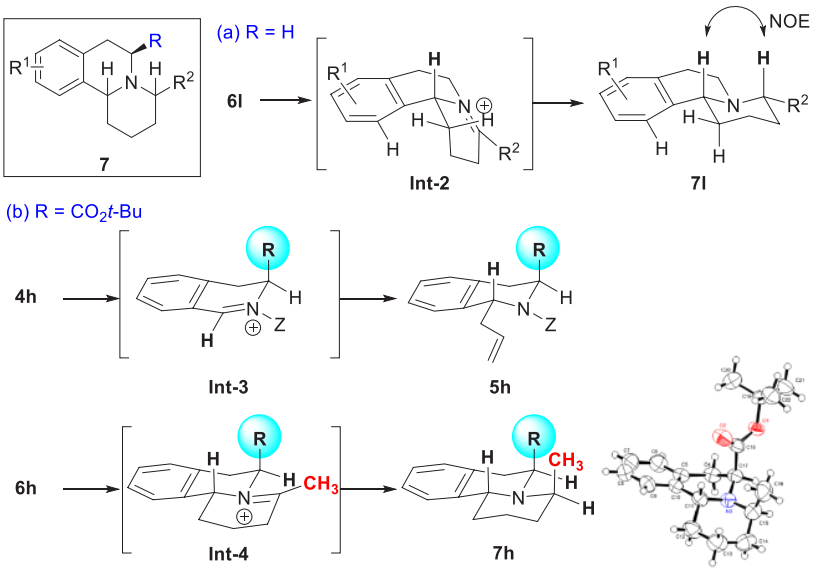

Figure 2. Plausible Mechanism for the Formation of **7**.

pressure using a rotary evaporator. Reactions were followed by TLC analysis using silica gel 60 F_{254} with fluorescent indicator using UV lamp and $KMnO_4$ 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 ^{13}C NMR spectra were measured with Bruker AVANCE III HD 400. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield to $CHCl_3$ (δ = 7.26), ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ 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. $CDCl_3$ 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-*p*-benzoquinone (DDQ) (3.7 mg, 0.016 mmol) in CH_2Cl_2 (0.8 mL) was added TFA (88 μL, 1.1 mmol) at room temperature. The mixture was stirred for 5 min under a air atmosphere. *N*-Cbz protected tetrahydroisoquinoline **4a** (44 mg, 0.16 mmol) in CH_2Cl_2 (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 O_2 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 $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ 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. R_f = 0.46 (hexane/EtOAc = 5:1). ^1H NMR (400 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{20}H_{22}NO_2$ $[M + H]^+$ 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 CH_2Cl_2 (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. R_f = 0.51 (hexane/EtOAc = 1:1). ^1H NMR (400 MHz, $CDCl_3$, 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), 3.38−3.23 (m, 1H), 3.01−2.87 (m, 1H), 2.79−2.70 (m, 3H), 2.16 and 2.07 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$, 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 $C_{22}H_{23}NNaO_3$ $[M + Na]^+$ 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(1*H*)-carboxylate **6a** (51 mg, 0.15 mmol) in MeOH (3.0 mL)/CH_2Cl_2 (0.6 mL) was added Pd/C 10 wt % (7.6 mg, 15 wt %). The reaction mixture was filled with hydrogen and 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 (CH_2Cl_2/MeOH = 10:1) to afford **7a** (23 mg, 80%) as yellowish oil. R_f =

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0.57 (CH_2Cl_2/MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.05 (m, 4H), 3.41−3.36 (m, 2H), 3.12−3.04 (m, 1H), 2.79−2.74 (m, 1H), 2.43 (m, 1H), 2.33 (td, J = 11.0, 4.0 Hz, 1H), 2.26−2.23 (m, 1H), 1.89−1.86 (m, 1H), 1.66−1.43 (m, 4H), 1.23 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 134.4, 128.6, 125.9, 125.6, 125.3, 63.5, 58.3, 45.0, 33.4, 31.1, 29.7, 24.8, 20.7. HRMS (ESI) m/z calcd for $C_{14}H_{20}N$ $[M + H]^+$ 202.1590, found 202.1591.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04154.

Experimental details for synthesis of **5**, **6**, and **7**; NOE experiments of **7l**; 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.

■ AUTHOR INFORMATION

Corresponding Author

Sun-Joon Min − *Department of Applied Chemistry, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea; Center for Bionano Intelligence Education and Research and Department of Chemical & Molecular Engineering, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea;* orcid.org/0000-0003-0867-4416; Email: sjmin@hanyang.ac.kr

Authors

Sunhwa Jung − *Department of Applied Chemistry, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea; Center for Bionano Intelligence Education and Research, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea*

Seungri Yoon − *Department of Applied Chemistry, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea; Center for Bionano Intelligence Education and Research, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea*

Jae Kyun Lee − *Brain Science Institute, Korea Institute of Science and Technology (KIST), Seoul 02792, Republic of Korea;* orcid.org/0000-0003-0587-5319

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c04154

Notes

The authors declare no competing financial interest.

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