Tandem C–H oxidation/cyclization/rearrangement and its application to asymmetric syntheses of (−)-brussonol and (−)-przewalskine E

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Natural products are a vital source of lead compounds in drug discovery. Development of efficient tandem reactions to build useful compounds and apply them to the synthesis of natural products is not only a significant challenge but also an important goal for chemists. Here we describe a tandem C–H oxidation/cyclization/rearrangement of isochroman-derived allylic silyl ethers, promoted by DDQ and InCl₃. This method allows the efficient construction of tricyclic benzoxa[3.2.1]octanes with a wide substrate scope. We employ this tandem reaction to achieve the asymmetric total syntheses of (−)-brussonol and (−)-przewalskine E.
The strained tricyclic benzoxa[3.2.1]octane skeleton exists in numerous bioactive and pharmaceutical molecules such as przewalskone and brussonol, and it is a useful building block in organic synthesis such as for producing platensimycin (Fig. 1a). In recent decades, the significant biological activity and potential pharmaceutical value of molecules with this skeleton have driven chemists to devise several methods for constructing it (Fig. 1b). Nevertheless, more efficient and practical methods are needed.

One possible approach is the C–C bond formation via direct (sp³) α-C–H bond functionalization, which is increasingly being used to synthesize complex N- or O-containing molecules. While several reactions have been described to achieve C–C formation at the α-position in amines, only a handful of reactions have been reported for C–C formation in ethers. In connection with our long-standing interest in α-C–H bond functionalization of ethers and carbon–carbon rearrangement of allylic alcohol/silylether, we speculated that it might be possible to construct the benzoxa[3.2.1]octane unit via a tandem reaction that is initiated by benzylic C–H oxidation of an isochroman-derived allylic silyl ether and triggered by C–C bond rearrangement.

Here we use 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and InCl₃ to promote tandem C–H oxidation/cyclization/rearrangement of isochroman-derived allylic silylether. We then apply this efficient tandem reaction to asymmetric syntheses of the bioactive natural products (−)-brussonol and (−)-przewalskine.

**Results**

**Reaction optimization.** We began our efforts to generate the benzoxa[3.2.1]octane unit using the model substrate 1a, prepared as a single diastereoisomer in a general procedure.
Initial experiment with the common oxidant DDQ (2.0 equiv.) as the sole promoter failed to give the desired product and resulted in fully recovery of 1a (Table 1, entry 1). Next we tried combinations of DDQ (1.2 equiv.) and Lewis acids in the presence of 4-Å molecular sieves. Using FeCl3 or SnCl4 led to the decomposition of 1a (entries 2 and 3), whereas using SnBr4 led to the consumption of 1a in 8 h and the desired product 2a in 33% yield (entry 4). Cu(OTf)2 and LiClO4 also promoted this transformation, albeit in lower yield (entries 5 and 6). When 1.0 equiv. InCl3 was used, 2a was obtained in 36% yield after 24 h and 15% of 1a was recovered (entry 7). Increasing the load of DDQ to 2.0 equiv. gave higher yield (56%) in shorter time (4 h). Interestingly, decreasing the load of InCl3 to 0.1 equiv. further increased the yield of 2a to 69% (entry 9). The molecular sieve was essential to this reaction, since omitting it led to only 30% yield (entry 10). With InCl3 as the catalyst, a side reaction in which 1a was partially desilylated to give free allylic alcohol was always observed. To inhibit this, we screened several weakly basic additives (entries 11–14). We were pleased to find that using 2,6-dibromopyridine (DBP, 5.0 equiv.) significantly improved yield to 81% (entry 14).

### Table 1 | Conditions optimization*.

| Entry | Cat. (equiv.) | DDQ (equiv.) | Base (equiv.) | Time (h) | Yield† |
|-------|---------------|-------------|--------------|----------|--------|
| 1     | —             | 2.0         | —            | 12       | NR     |
| 2     | FeCl3/1.0     | 1.2         | —            | 0.5      | Dec    |
| 3     | SnCl4/1.0     | 1.2         | —            | 0.5      | Dec    |
| 4     | SnBr4/1.0     | 1.2         | —            | 8        | 33%    |
| 5     | Cu(OTf)2/1.0  | 1.2         | —            | 12       | 23%    |
| 6     | LiClO4 (1.0)  | 1.2         | —            | 12       | 29%    |
| 7     | InCl3 (1.0)   | 1.2         | —            | 24       | 36%    |
| 8     | InCl3 (1.0)   | 2.0         | —            | 12       | 36%    |
| 9     | InCl3 (0.1)   | 2.0         | —            | 12       | 30%    |
| 10‡   | InCl3 (0.1)   | 2.0         | Na2CO3       | 12       | 44%    |
| 11‡   | InCl3 (0.1)   | 2.0         | Et3N         | 12       | NR     |
| 12‡   | InCl3 (0.1)   | 2.0         | DBTBP        | 12       | Trace  |
| 13§   | InCl3 (0.1)   | 2.0         | DTBP         | 12       | 81%    |
| 14§   | InCl3 (0.1)   | 2.0         | DBP          | 12       | 81%    |

*All reactions unless specifically notified were performed with 0.3 mmol 1a and 150 mg 4 Å MS in 3.0 ml CH2Cl2 at RT.
†Isolated yield.
‡No 4 Å MS used.
§0.5 equiv. base used.

(see Supplementary Methods 1 and Supplementary Data 1 and 4). Initial experiment with the common oxidant DDQ (2.0 equiv.) as the sole promoter failed to give the desired product and resulted in fully recovery of 1a (Table 1, entry 1). Next we tried combinations of DDQ (1.2 equiv.) and Lewis acids in the presence of 4-Å molecular sieves. Using FeCl3 or SnCl4 led to the decomposition of 1a (entries 2 and 3), whereas using SnBr4 led to the consumption of 1a in 8 h and the desired product 2a in 33% yield (entry 4). Cu(OTf)2 and LiClO4 also promoted this transformation, albeit in lower yield (entries 5 and 6). When 1.0 equiv. InCl3 was used, 2a was obtained in 36% yield after 24 h and 15% of 1a was recovered (entry 7). Increasing the load of DDQ to 2.0 equiv. gave higher yield (56%) in shorter time (4 h). Interestingly, decreasing the load of InCl3 to 0.1 equiv. further increased the yield of 2a to 69% (entry 9). The molecular sieve was essential to this reaction, since omitting it led to only 30% yield (entry 10). With InCl3 as the catalyst, a side reaction in which 1a was partially desilylated to give free allylic alcohol was always observed. To inhibit this, we screened several weakly basic additives (entries 11–14). We were pleased to find that using 2,6-dibromopyridine (DBP, 5.0 equiv.) significantly improved yield to 81% (entry 14).

In addition, the reaction was also carried out in some other solvents (C2H4Cl2, CH3NO2, CH3CN, toluene, tetrahydrofuran (THF)) and oxidants (TEMPO, benzoquinone), but results were not better than with CH2Cl2 and DDQ. Therefore, the optimal conditions were defined to be DDQ (2.0 equiv.), InCl3 (0.1 equiv.), DBP (5.0 equiv.) and 4-Å molecular sieve in CH2Cl2 (entry 14, see Supplementary Methods 2).

### Substrate scope.

Using these optimal reaction conditions, we tested the substrate scope of this transformation extensively (Fig. 2), starting with the allylic substituents at R1. Substrates 1b and 1c with n-butyli and i-propyl groups at this position reacted well and gave the desired products 2b and 2c in respective yields of 80 and 83%. Benzy1-substituted 1d also afforded the desired product 2d in good 72% yield. In contrast, substrates with more electron-rich groups at R1 gave only medium to good yields. For example, substrates 1e and 1f with phenyl and vinyl substituents gave the corresponding products 2e and 2f in respective yields of 74 and 63% yield. The substrate 1g with an acetylenyl substituent generated the product 2g in a lower yield of 23%. Using substrate 1h with a methyl substitution at the allylic (C=C) led to smooth production of 2h with a quaternary stereocenter in 83% yield. The product’s relative configuration was confirmed by X-ray diffraction analysis. Next, the substituent effects on the aromatic ring of the isochroman moiety were investigated—compounds 1i and 1j fully substituted with MeO or Me reacted well, giving products 2i and 2j in respective yields of 83 and 87%. These relatively high yields may mean that the electron-donating methoxy group stabilizes the benzylic oxonium carbocation in the transition state in Fig. 1c better than hydrogen does. Compound 1k with a bromo substituent at the 7th position in the isochroman moiety led to the desired product 2k in 63% yield, extending the flexibility of our approach for further derivatization.

We also expanded the substrate scope to acyclic systems to allow the synthesis of multi-substituted THF derivatives, which exist in numerous bioactive and pharmaceutical molecules. Four representative allylic silyl ethers 1l–1o with terminal benzylic or allylic ethers as the reaction trigger generated the corresponding products 2l–2o in 37–53% yields under the same optimal conditions. Notably, the reaction was triggered efficiently by either benzylic ethers (1l, 1m, 1o) or cinnamyl ethers. (1n) When a TBDPS ethylene ether was created in 1o to compete with benzy1 ether during the expected reaction, only the benzy1 ether underwent reaction, affording the product 2o in 42% yield. Under the same optimal conditions, yields were generally lower with acyclic substrates than with cyclic ones, which may be due to hyperoxidation of THF products that produced furan-type byproducts (Supplementary Methods 2.2).

### Asymmetric syntheses of (−)-brussonol and (−)-przewalskine E.

To further demonstrate the utility of this novel method for synthesizing polycyclic molecules, we applied it to the total synthesis of two important bioactive natural products—tetracyclic (−)-przewalskine E (3a) and (−)-brussonol (3b). Two diastereoselective routes to 3b have been reported by Sarpong and Jennings, while its asymmetric synthesis has been achieved by Majetich. We are unaware of reports of the synthesis of 3a.
In our retrosynthetic analysis (Fig. 3), we hypothesized that we could generate \(3a\) from \(3b\) via biomimetic oxidation, and that \(3b\) could be obtained from ketone intermediate \(3c\). We planned to construct rings C and D in \(3c\) by applying our novel method to the tricyclic allylic siylether \(3d\), which could be obtained from achiral allylic alcohol \(3e\) via a challenging tandem Sharpless asymmetric epoxidation/epoxy opening. The precursor \(3e\) could be prepared from the simple starting material \(3f\) in a few short steps.

On the basis of this strategy, we started our synthesis by preparing allylic alcohol \(3e\) from bromide \(3f\) (Fig. 4), which was formalized and protected as a 1,3-dioxane \(3g\) to survive subsequent metallization\(^{45,46}\). Deprotonation of \(3g\) with \(n\)-BuLi followed by quenching with formaldehyde and finally bromination of the resulting hydroxyl group with \(Ph_3P/\text{CBr}_4\) gave benzyl bromide \(3h\) in 41% yield over two steps. Coupling bromide \(3h\) with vinyl triflate \(3i\) and then removing the 1,3-dioxane protecting group in aqueous HCl afforded aldehyde \(3j\) in 69% yield over two steps. Excess diisobutylaluminum hydride (DIBAL-H) was used to reduce \(3j\) in a single step to diol \(3e\) in 93% yield. Then we investigated the key tandem Sharpless asymmetric epoxidation/epoxy opening of \(3e\). The expected tricyclic species \(3k\) was obtained in 90% yield and 83% ee in the presence of classic Sharpless catalyst (1.5 equiv.) at \(-50^\circ\text{C}\). While this enantioselectivity is not ideal, it appears to be a rare example of successful tetra-substituted olefin epoxidation\(^{48}\). Selective oxidation of the primary hydroxyl of \(3k\) followed by methylenenation afforded the desired tertiary allylic alcohol \(3l\), which was protected to give the precursor \(3d\). Fortunately, our optimal conditions of oxidative cyclization/ring enlargement gave the expected tetracyclic skeleton \(3c\) in high yield (81%) and excellent stereoselectivity, no other isomer was detected.

At this stage, only the installation of a gem-dimethyl group remained to complete the synthesis of \(3b\). Initial attempts to

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**Figure 2 | Reaction scope**. *All reactions unless notified were performed in experimental section procedure on a 0.1–1.5 mmol substrate scale in CH\(_2\)Cl\(_2\) (0.1 mmol ml\(^{-1}\)), 0.1 equiv. InCl\(_3\), 4 Å MS (50 mg per 0.1 mmol), 2.0 equiv. DDQ, 5.0 equiv. DBP at RT. Relative configuration of the products were assigned based on X-ray structure of \(2h\) and \(2j\) (CCDC 1000811, CCDC 1000827, See Supplementary Data 2 and 3 for more details). **Isolated yields. ***1.1 equiv. DDQ was used.

**Figure 3 | Retrosynthetic analysis of \(3a, b\).** The current method was used to construct the core framework.
transform the carbonyl in ketone 3c directly into gem-dimethyl using TiMe2Cl2 reagent49 gave the desired product 3o in low yield. Therefore, we adopted a three-step protocol involving Wittig reaction, cyclopropanation and reduction. Treating 3c with Ph3PCH3Br/t-BuOK followed by Simmons–Smith cyclopropanation of the resulting exo-cyclic olefin gave the cyclopropane compound 3n, which was hydrogenated with H2 (1 atm)/PtO2 to afford the desired 3o in 45% yield over three steps50. Demethylating 3o using with EtSNa/DMF provided natural product 3b in 76% yield, and the spectral data were identical to those reported by Sarpong41 (Supplementary Tables 1 and 2). We screened various oxidants for the biomimetic oxidation of 3b to 3a; Ag2O proved to be the best, affording the natural product 3a in 71% yield. Its spectral data were identical to those reported by Zhao40 (Supplementary Tables 3 and 4).

**Discussion**

The tandem C–H oxidation/cyclization/rearrangement of isocroman-derived allylic silylether described here shows good chemo- and stereoselectivity as well as good product yield. We demonstrated the usefulness of this approach by using it to achieve the asymmetric total syntheses of (−)-brussonol and
acetal rearrangement under acidic conditions via alkoxy release preparation as well as milder reaction conditions than a similar additional applications in organic synthesis.

One is a tandem cyclization/semipinacol rearrangement to oxocarbenium cation under oxidative conditions (Fig. 5).

In addition, both substrates methods under our optimal conditions needs to be confirmed.

Data were measured using the electrospray ionization technique on a Fourier transform infrared spectrometer. High-resolution mass spectral analysis trimethylsilane as the internal standard. Infrared spectra were recorded on a high-performance liquid chromatography traces, see Supplementary Figs 137 and 23.

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Author contributions
Z.-W.J. conducted most of the experiments; Q.Z. prepared substrates for reaction scope evaluation and synthesis of (−)-brussonol and (−)-pyrrole and E; W.-X.L. and S.J. (Wuyi University) prepared some substrates for reaction scope evaluation; Y.-Q.T., F.-M.Z., S.-H.W. and S.-Y.Z. conceptualized and directed the project, and prepared the manuscript with the assistance from all co-authors.

Additional information
Accesion codes: The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 1000817, 1000816, 1008811 and 1008827. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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