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Redox-Neutral α-C−H Functionalization of Pyrrolidin-3-ol

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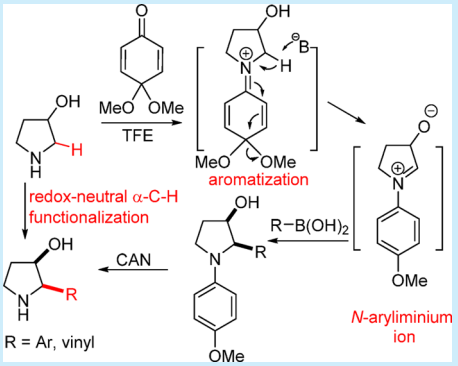
Supporting Information

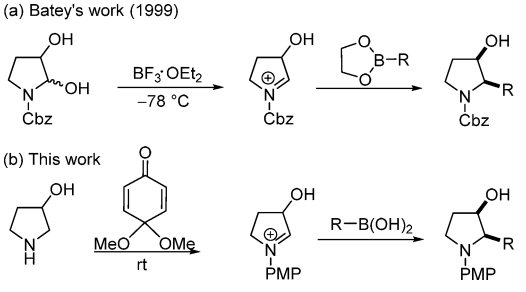
ABSTRACT: A redox-neutral α-C−H oxygenation of commercially available pyrrolidin-3-ol with a monoprotected *p*-quinone generated an *N*-aryliminium ion intermediate, which reacted in situ with boronic acid nucleophiles to produce a series of *cis*-2-substituted pyrrolidin-3-ols. With this strategy, 8-*epi*-(−)-lentiginosine was synthesized from (3*R*,4*R*)-pyrrolidine-3,4-diol in three steps.



The 2-substituted pyrrolidin-3-ol moiety is found in many biologically active natural products, including indolizidine and pyrrolizidine alkaloids.[1] Most of the strategies for synthesis of this moiety involve pyrrolidine ring closure of open-chain precursors.[1,2] Therefore, to synthesize a series of α-substituted pyrrolidine derivatives, one must separately prepare precursors with different α-substituents and then perform the ring closure. In 1999, Batey and co-workers successfully utilized *N*-Cbz-protected 2,3-dihydroxy pyrrolidine as an *N*-acyliminium ion precursor for the synthesis of α-substituted pyrrolidines; in the presence of boron trifluoride, this precursor reacted with various alkenylboronates or arylboronates to give α-substituted pyrrolidin-3-ols in very high yields (see Scheme 1a).[3a] They further demonstrated the utility of their method for the simplification of pyrrolidine alkaloid synthesis.[3]

The direct functionalization of the α-C−H of pyrrolidine or pyrrolidine derivatives is a concise way to synthesize α-substituted pyrrolidines. In recent years, many pyrrolidine α-C−H functionalization strategies have been developed,[4,5] including various elegant methods that offer special redox and atom economy.[6,7] In this study, we started from commercially available pyrrolidin-3-ol hydrochloride (**1**), which was subjected to redox-neutral α-C−H oxygenation to form an *N*-aryliminium ion intermediate that was then allowed to react with boronic acids or boronates to produce a series of *cis*-2-substituted pyrrolidin-3-ols (Scheme 1b).

Scheme 1. Functionalization of the α-Position of Pyrrolidines via Iminium Ion Formation



In previous work, we showed that pyrrolidine reacts with *o*-benzoquinone in 2,2,2-trifluoroethanol (TFE) to give an *N*,*O*-acetal, which can then undergo ring opening by a Grignard reagent to introduce a substituent at the α-position.[7l] In this study, we began by exploring the use of 3,5-di-*tert*-butyl-1,2-benzoquinone to oxidize pyrrolidin-3-ol (**1**) in TFE (Table 1, entry 1). Although an *N*,*O*-acetal was formed, as in our previous work,[5j] the acetal did not react with the boron nucleophile (*E*)-styrylboronic acid (**2a**). To prevent generation of the *N*,*O*-acetal, we switched to 2,6-di-*tert*-butyl-1,4-benzoquinone as the oxidant, but the reaction gave a complicated mixture of products (entry 2 in Table 1). Next, we tried using a more weakly oxidizing monoprotected *p*-quinone, such as 4,4-dimethoxycyclohexa-2,5-dien-1-one, we successfully obtained desired product **3a** in high yield by using an excessive amount of **1** (entry 3 in Table 1). However, under this condition, pyrrolidine or piperidin-3-ol did not react in the same way. Using this oxidant, we evaluated solvents other than TFE. In THF, the desired reaction did not occur, and most of the starting material was recovered (entry 4 in Table 1). In another fluorinated alcohol, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), the yield of **3a** was only 37% after 24 h (entry 5 in Table 1); and reaction in a nonfluorinated alcohol (ethanol) afforded only a 27% yield of the product (entry 6 in Table 1). The fact that TFE was the best solvent may have been due to its ability to stabilize the iminium ion intermediate.[8] The

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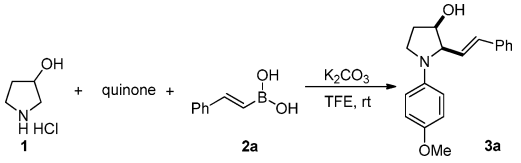
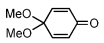
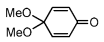
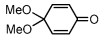
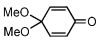
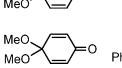
Table 1. Oxidation/Nucleophilic Addition Reactions of Pyrrolidin-3-ol (1)[a]



entry	quinones, solvents, and boronic reagent	yield (%)[b]
1		nd
2		nd
3		93
4	 THF instead of TFE	0
5	 HFIP instead of TFE	37
6	 EtOH instead of TFE	27
7	 instead of **2a**	85

[a]Reaction conditions: **1** (0.3 mmol), quinone (0.2 mmol), (*E*)-styrylboronic acid (**2a**, 0.3 mmol), and K_2CO_3 (0.31 mmol) in solvent (4 mL) were stirred at room temperature (rt) for 12 h. [b]Isolated yields are reported.

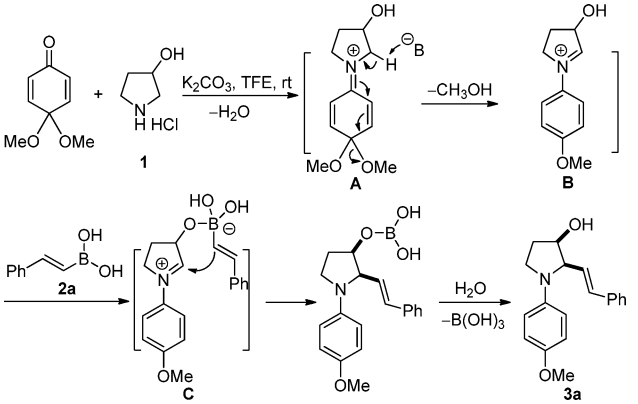
reason for the lower yield in the hexafluorinated alcohol, which has even higher ionizing power than TFE, may have been that its higher pK_a interfered with nucleophilic addition of the amine to the quinone. Because organic boronates are sometimes easier to prepare than the corresponding boronic acids, we also evaluated the use of pinacol boronate as a nucleophile; however, under these conditions, we observed a slight decrease in the chemical yield (to 85%, entry 7 in Table 1).

The protons at the 2- and 3-positions of **3a** showed correlation in the two-dimensional NOESY spectrum, indicating a *cis* relationship between the substituents at these two positions. We also prepared *trans* diastereomer **3a′** by means of a Mitsunobu reaction of **3a** (see the Supporting Information (SI)), and comparison of the ^{1}H NMR spectrum of the crude product of the oxidation/nucleophilic addition reaction with the spectrum of **3a′** confirmed that the *trans* isomer was not produced in the reaction.

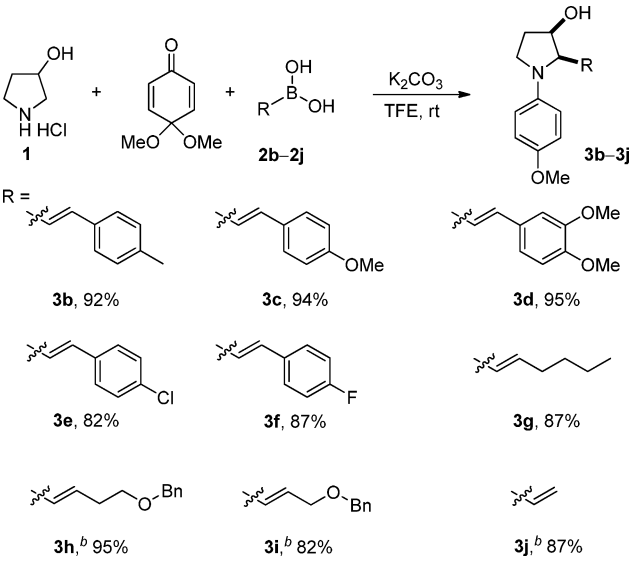
Based on the above-described evidence, we propose the mechanism outlined in Scheme 2. Nucleophilic attack of the N atom of pyrrolidin-3-ol on the quinone generates iminium ion **A**, and subsequent α-proton abstraction followed by aromatization of the quinone moiety and loss of methanol produces iminium ion **B**.[9] The hydroxy group at the 3-position of **B** coordinates with styrylboronic acid (**2a**) to generate transient species **C**, which undergoes nucleophilic attack by the double bond from the same face as the 3-hydroxyl group to afford *cis*-2-substituted pyrrolin-3-ol (**3a**) as the only stereoisomer.[3a,10]

Using the optimized reaction conditions (Table 1, entry 3), we investigated various vinyl boronic acid nucleophiles (Scheme 3). Substituted styrenyl boronic acids, alkyl boronic acids, and boronates all gave the desired products in high yields (82%–95%). Note that our approach to the synthesis of **3j**, which is the key intermediate in a total synthesis of the alkaloid loline,[11] is more simple than the procedure reported in the literature. The *p*-

Scheme 2. Proposed Mechanism for Oxidation/Nucleophilic Addition Reactions of Pyrrolidin-3-ol (1)



Scheme 3. Oxidation/Nucleophilic Addition Reactions of Pyrrolidin-3-ol (1) Using Vinyl Boronic Acids or Boronates[a,b]



[a]Reaction conditions: **1** (0.3 mmol), quinone (0.2 mmol), vinyl boronic acid (**2**, 0.3 mmol), and K_2CO_3 (0.31 mmol) were stirred in TFE (4 mL) at rt. [b]Pinacol vinyl boronate was used instead of a vinyl boronic acid.

methoxyphenyl group of products **3** could be removed by oxidation with CAN to afford the corresponding free amines (see the SI).

We previously found that, although we could introduce alkyl groups at the α-position of pyrrolidine via reaction of *N*,*O*-acetals with Grignard reagents,[7] α-benzyl-substituted pyrrolidines generated by reactions with benzyl Grignard reagents underwent oxidation in air and cyclization to form *N*,*O*-acetals. Therefore, in the current study, we explored α-C–H arylation of pyrrolidin-3-ol under the same reaction conditions used for the corresponding alkylation reactions (Scheme 4). Aryl boronic acids with electron-donating groups gave high yields of the desired products (**3l**–**3p**), and aryl boronic acids with electron-withdrawing groups also performed well (**3q**–**3s**). The *cis* configuration of the pyrrolidine substituents was confirmed by X-ray crystal analysis of **4r**, the Ts ester of **3r**.[12] We found that the 3-hydroxy group was essential for the relative stability of the product (especially when an electron-rich aryl group was present), presumably by

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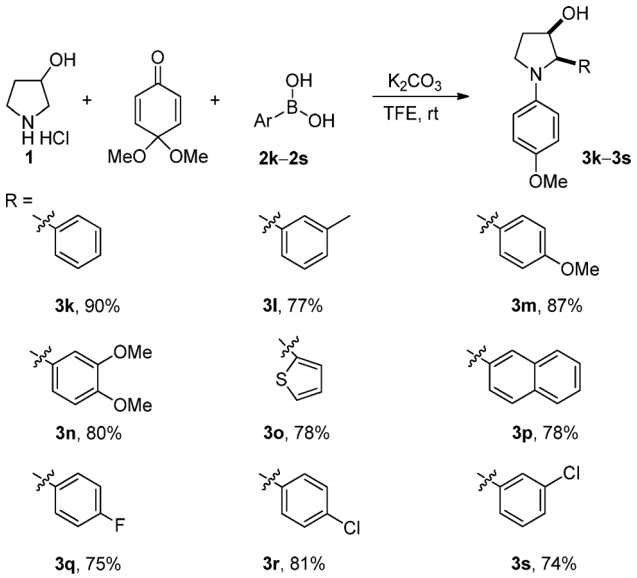
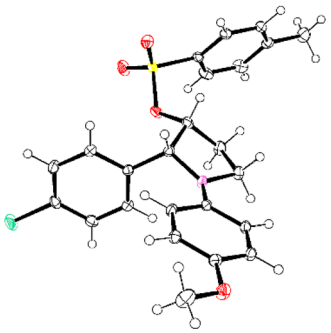
Scheme 4. Oxidation/Nucleophilic Addition Reactions of Pyrrolidin-3-ol (1) Using Aryl Boronic Acids[a]





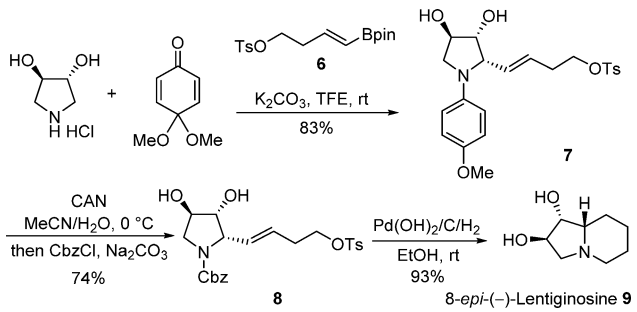
X-ray structure of **4r**, the Ts ester of **3r**

[a]Reaction conditions: **1** (0.3 mmol), quinone (0.2 mmol), aryl boronic acid (**2**, 0.3 mmol), and K_2CO_3 (0.31 mmol) were stirred in TFE (4 mL) at rt.

formation of a hydrogen bond with the N atom. If the 3-hydroxy group of **3n** was protected with a MOM group, the resulting compound was unstable in air and was quickly oxidized to a complicated mixture of dark-colored products.

Finally, we evaluated the utility of our reaction protocol by using it in a total synthesis of 8-*epi*-(−)-lentiginosine (**9**, Scheme 5). The indolizidine alkaloid (−)-lentiginosine exhibits excellent anti-HIV, antitumor, and immune-modulating activities, in addition to inhibiting amyloglycosidases (IC_{50} = 5 μg mL^{-1}). More than 40 total syntheses of lentiginosine and its analogues have been achieved.[13] In addition, 11 synthetic routes to 8-*epi*-(−)-lentiginosine, which inhibits β-glucosidase and β-xylanase,[14] have been reported.[14,15] We started a synthesis 8-*epi*-(−)-lentiginosine from commercially available (3*R*,4*R*)-pyrrolidine-3,4-diol hydrochloride, which was allowed to react with 4,4-dimethoxycyclohexa-2,5-dien-1-one and Ts-protected boronate **6** to give *cis*-2-substituted pyrrolidine **7** in 83% yield. Removal of the *N*-*p*-methoxylphenyl group with CAN gave the free amine, which was too polar to be isolated and was therefore trapped with a readily removable Cbz protecting group to afford **8**. Under hydrogenation conditions, the double bond was reduced and the Cbz group was removed, at which point the free amine cyclized spontaneously to give 8-*epi*-(−)-lentiginosine **9**.

Scheme 5. Synthesis of 8-*epi*-(−)-Lentiginosine



In summary, we have developed a protocol for mild redox-triggered α-C−H functionalization of pyrrolidin-3-ol to generate an *N*-aryliminium ion intermediate, which can then react with boronic acids or boronates. The protocol was used to synthesize *cis*-2-substituted pyrrolidin-3-ols with various substituents in high yields, and its utility was demonstrated by means of a facile synthesis of 8-*epi*-(−)-lentiginosine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03807.

Experimental details, characterization data for new compounds, copies of NMR spectra and high-resolution mass spectra, and X-ray crystallographic data of **4r** (PDF)

Accession Codes

CCDC 1510783 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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