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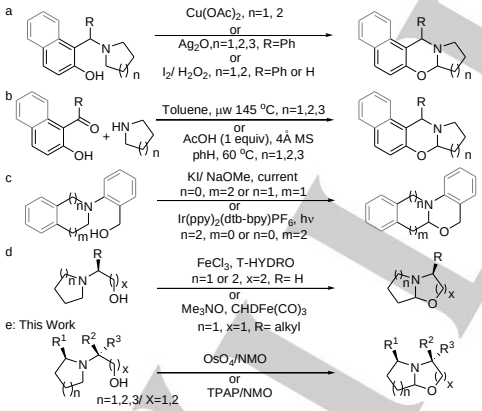
# C-H Functionalization of Amino Alcohols by Osmium Tetroxide/NMO or TPAP/NMO: Protecting Group-Free Synthesis of Indolizidines (–)-223AB and 3-*epi*-(–)-223AB

Wei-Lun Chen,[a] Lee-Ya Wang,[a] and Yu-Jang Li*[a]

**Abstract:** The oxidative cyclization of amino alcohols by osmium tetroxide/NMO or tetrapropylammonium perruthenate (TPAP)/NMO was found to provide an N,O-acetal moiety through the trapping of the resulting iminium ion by the alcohol. These two transformations were demonstrated in the synthesis of indolizidines (–)-223AB and 3-*epi*-(–)-223AB.

The functionalization of a carbon adjacent to a tertiary amine nitrogen via a C($sp^3$)-H activation has been developed over the past decade, and such methods include oxidative cross-dehydrogenative coupling (CDC) reactions,[1,2] electro-oxidative activations and photoredox reactions.[3,4] In these processes, the generated iminium cations are important intermediates for the subsequent C-C, C-O and C-N bond formations. In particular, the formation of a C-O bond by the addition of an oxygen nucleophile to the iminium cation gives an N,O-acetal moiety. Such manipulation can simultaneously activate and protect a specific carbon, thus providing greater efficiency and flexibility for subsequent synthetic transformations. Since the N,O-acetal moiety can be assembled or cleaved whenever carbon activation or subsequent functionalization is needed, tedious protection/deprotection steps in the synthetic sequence can be avoided.




**Scheme 1.** Formation of cyclic N,O-acetals: a) oxidation involving phenolic alcohols; b) metal and oxidant free conditions; c) formation by electrooxidation and photooxidation processes; d) oxidation from saturated amino alcohols; e) oxidation by $OsO_4$/NMO or TPAP/NMO.

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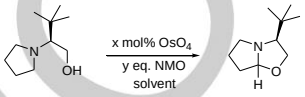
**Table 1.** Reaction conditions for the oxidation of **1a** with $OsO_4$/NMO.[a]




**1a** **2a/3a**

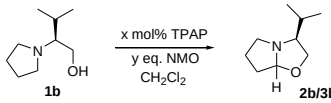
| Entry | $OsO_4$, mol% | NMO, eq | Yield (%)[b] |
|---|---|---|---|
| 1 | 2 | 1 | 60 (28) |
| 2 | 2 | 2 | 62 (23) |
| 3 | 2 | 3 | 80 |
| 4 | 4 | 3 | 89 |
| 5 | 6 | 3 | 88 |
| 6[c] | 4 | 3 | 60 |
| 7 | 1 | 3 | 64 (28) |
| 8 | 0.1 | 3 | 55 (36) |
| 9 | 0 | 3 | N.R. |
| 10 | 100 | 0 | 8 |

[a] Unless otherwise indicated, the reaction was carried out using 0.4 mmol of **1a** (0.3 M) in THF/$H_2O$ (10:1), $OsO_4$ (2.5% in *t*-BuOH) was added at ambient temperature, and the mixture was stirred for 1 hour. [b] The isolated yield, with the yield of recovered **1a** shown in parentheses. [c] ACN/$H_2O$ (10:1) as the reaction solvent.

Unfortunately, existing N,O-acetal generation strategies involving the trapping of oxygen by the iminium cation are better suited to the addition of phenolic oxygens via $Cu(OAc)_2$, $Ag_2O$ or $I_2/H_2O_2$ mediated oxidations (Scheme 1a),[5,6,7] or reactions of aryl aldehydes/aryl alkyl ketones with amines under metal and oxidant free conditions (Scheme 1b).[8] The limited examples involving nonphenolic hydroxyl groups include the electro-oxidative cyclization or $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ catalyzed photooxidation of hydroquinoyl and hydroisoquinoyl alcohols (Scheme 1c),[4b,4c] and $FeCl_3$[9] or $CHDFe(CO)_3$[10] mediated oxidations of saturated amino alcohols (Scheme 1d). Herein, we disclosed two novel and general procedures for the oxidative cyclization of saturated amino alcohols. When amino alcohols **1a** and **1b** were used as test substrates, we were surprised to find that a catalytic amount of $OsO_4$ with NMO or a catalytic amount of tetrapropylammonium perruthenate (TPAP) with NMO are efficient reagents for this transformation (Scheme 1e). Although studies related to the oxidation of tertiary amines by $OsO_4$ or ruthenium oxidants have been reported, oxidations with $OsO_4$ generally resulted in complicated mixtures of amides,[11] and oxidations using $RuCl_2(PPh_3)_3$/*t*-BuOOH or $RuCl_3/O_2$/NaCN gave the corresponding α-oxygenation or α-cyanation products,[12] studies related to the intramolecular trapping of alcohols to form N,O-acetals involving the use of $OsO_4$ or ruthenium oxidants have not been reported. In our initial study of $OsO_4$/NMO (Table 1), treatment of **1a** with $OsO_4$ (2 mol%) and NMO (1 eq) provided a mixture of isomers **2a/3a**

in 60%. When the amount of NMO was increased to 2 and 3 equivalents, the products were obtained in 62% and 80% yields, respectively (Entries 2 and 3). Increasing the loading of $OsO_4$ (4-6 mol%) also improved the yield from 80% to approximately 88-89% (Entries 4-5), but the effect was not as great as that of increasing the NMO loading. Changing the solvent from THF to acetonitrile gave a lower yield (60%). When the $OsO_4$ loading was decreased to 1 and 0.1 mol%, the products were obtained in 64% and 55% yields, respectively (Entries 7 and 8). In the absence of $OsO_4$, no reaction occurred (Entry 9). Nevertheless, when one equivalent of $OsO_4$ but no NMO was used in the reaction, the reaction proceeded slowly and provided the products in 8% yield (Entry 10).

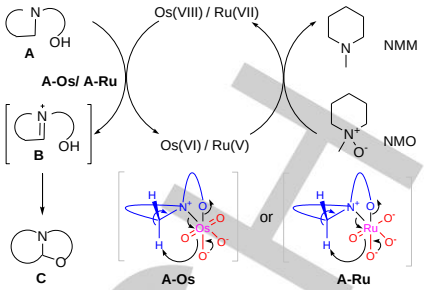
**Table 2.** Reaction conditions for the oxidation of **1b** with TPAP/NMO.[a]




| Entry | TPAP, mol% | NMO, eq | T (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 1 | 2 | 2 | 23 (43) |
| 2 | 2 | 2 | 2 | 50 (18) |
| 3 | 2 | 2 | 4 | 75 |
| 4 | 5 | 2 | 4 | 75 |
| 5 | 8 | 2 | 4 | 76 |
| 6 | 100 | 0 | 4 | 19 (45) |

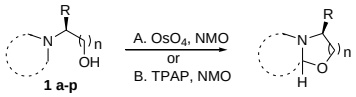
[a] The reaction was carried out using 0.4 mmol of **1b** (0.3 M) in $CH_2Cl_2$, and TPAP was added at ambient temperature. [b] The isolated yield with the yield of recovered **1b** shown in parentheses.

When studied under TPAP/NMO conditions (Table 2), the treatment of **1b** with TPAP (1 mol%) and NMO (2 eq) for 2 hours provided **2b/3b** in 23% yield, and 43% of **2a** was recovered (Entry 1). When 2 mol% TPAP was used, the yield increased to 50%, but 18% of **1b** remained (Entry 2). By increasing the reaction time to 4 hours, the products were obtained in 75% yield (Entry 3). Increasing the TPAP loading to 5 mol% and 8 mol% did not further increase the yield, and the products were obtained in yields of 75% and 76%, respectively (Entries 4 and 5). When one equivalent of TPAP and no NMO were used, the reaction gave 19% of **2b/3b**, 30% of the corresponding aldehyde and 45% of recovered **1b** (Entry 6). The above two reactions showed that; 1) both $OsO_4$ and TPAP are required respectively for the transformation, and 2) a lower loading of TPAP relative to $OsO_4$ can provide complete conversion. A plausible mechanism (shown in Scheme 2) was proposed to explain the transformation facilitated by $OsO_4$ or $RuO_4^-$ with NMO. The amino alcohol (**A**) was oxidized by $OsO_4$ or $RuO_4^-$, via intramolecular (as shown in **A-Os/ A-Ru**) or intermolecular deprotonation by NMM to afford the iminium cation (**B**) and Os(VI) or Ru(V) species, respectively. The generated iminium cation (**B**) was cyclized by hydroxyl group to the N,O-acetal product (**C**), and Os(VI) or Ru(V) species were transformed back to $OsO_4$ and $RuO_4^-$ to re-enter the catalytic cycle by NMO.




**Scheme 2.** Plausible mechanism for the oxidative cyclization.

**Table 3.** Reaction conditions for the oxidation of **1a-p** with $OsO_4$/NMO and TPAP/NMO.[a]

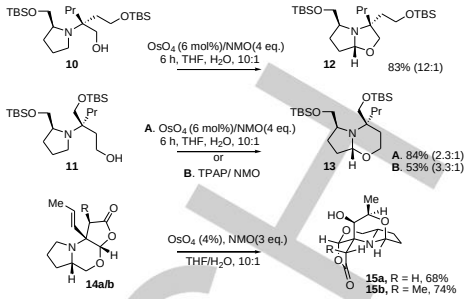



| Entry | Amine[b] | T (h) | Product[c] | Yield[%][d] |
|---|---|---|---|---|
| 1 | **1a** (R=*t*-Bu) | 1 | **2a/3a** | A. 89(100:0) |
| | | 0.75 | | B. 79(100:0) |
| 2 | **1b** (R=*i*-Pr) | 6 | **2b/3b** | A. 72(85:15) |
| | | 4 | | B. 75(83:17) |
| 3 | **1c** (R=*n*-Pr)[e] | 6 | **2c/3c** | A. 80(83:17) |
| | | 4 | | B. 82(83:17) |
| 4 | **1d** (R=*i*-Bu) | 6 | **2d/3d** | A. 75(81:19) |
| | | 4 | | B. 75(81:19) |
| 5 | **1e** (R=Bn) | 12 | **2e/3e** | A. 67(84:16) |
| | | 5 | | B. 65(85:15) |
| 6 | **1f** (R=Ph) | 12 | **2f/3f** | A. 65(80:20) |
| | | 5 | | B. 89(80:20) |
| 7 | **1g** (R=*t*-Bu) | 1 | **4g/5g** | A. 70 (41:59) |
| | | 3 | | B. 67 (40:60) |
| 8 | **1h** (R=*i*-Bu) | 4 | **4h/5h** | A. 65 (60:40) |
| | | 6 | | B. 70 (65:35) |
| 9 | **1i** (R=*i*-Pr) | 4 | **4i/5i** | A. 65 (67:33) |
| | | 6 | | B. 72 (67:33) |
| 10 | **1j** (R=Bn) | 6 | **4j/5j** | A. 70 (80:20) |
| | | 6 | | B. 67 (80:20) |
| 11 | **1k** (R=Ph) | 6 | **4k/5k** | A. 72 (91:9) |
| | | 6 | | B. 71 (88:12) |
| 12 | **1l** (R=*i*-Bu) | 0.5 | **6l/7l** | A. 71 (63:37) |
| | | 6 | | B. 69 (63:37) |
| 13 | **1m** (R=Bn) | 0.5 | **6m/7m** | A. 73 (65:35) |
| | | 6 | | B. 80 (62:38) |
| 14 | **1n** (R=Ph) | 0.5 | **6n/7n** | A. 75 (71:29) |
| | | 6 | | B. 72 (75:25) |
| 15 | **1o** | 24 | **8** + RCHO | A. 75 |
| | | 48 | | B. 45(81:19) [f] |
| 16 | **1p** | 24 | **9** + RCHO | A. 72 |
| | | 48 | | B. 36 (47:53) [f] |

[a] Conditions A: 0.4 mmol of substrate (0.3 M) in THF/$H_2O$ (10:1) and 4 mol% of $OsO_4$ (2.5% in *t*-BuOH) with 3 eq. of NMO; Conditions B: 0.4 mmol of substrate (0.3 M) in $CH_2Cl_2$ and 2 mol% of TPAP with 2 eq. of NMO. [b]. Unless otherwise indicated, *S* isomers were used. For the synthesis of **1a**-**p**, see the ESI. [c] Relative configurations of the two diastereomers were determined by 2D-NOESY analysis (see the ESI). [d] Yield of the isolated product after column chromatography, the diastereomeric ratios were determined by $^1$H NMR (400 MHz) analysis. [e] The *R* isomer was used. [f] Ratio of product to aldehyde as determined by $^1$H NMR.

We subsequently explored the substrate scope of the reaction with cyclic amines with different substituents and ring sizes (Table 3). The reactions of various substituted amino alcohols, including pyrrolidineethanols **1a**-**1f,** piperidineethanols **1g**-**1k** and azepaneethanols **1l-n** with 4 mol% $OsO_4$ and 3 eq. NMO (conditions A) and with 2 mol% TPAP and 2 eq. NMO (conditions B) afforded oxidative cyclization products **2a/3a** to **6n/7n** in moderate to good yields (Entries1-14). Notably, 1) TPAP/NMO conditions were found to be more effective than $OsO_4$/NMO conditions in the oxidative cyclization of five-membered ring pyrrolidineethanols **1a-f**, 2) the rates of the oxidative cyclizations under $OsO_4$/NMO conditions were proportional to the size of the nitrogen-containing ring, that is, azepane ring > piperidine ring > pyrrolidine ring, which indicated that the greater conformational flexibility is beneficial to the oxidation process, and 3) the rates of the oxidative cyclizations under TPAP/NMO conditions were less sensitive to the size of the nitrogen-containing ring, which might due to the less bulky volume of ruthenium oxide relative to osmium oxide. The reactions of homologous alcohols **1o** and **1p** under $OsO_4$/NMO conditions gave moderate yields (Entries 15 and 16), due to entropy, they reacted much more slowly than **1f** and **1k**, respectively (Entries 6 and 11); the reactions gave significantly lower yields under TPAP/NMO conditions. In both cases, cinnamaldehyde was obtained via the elimination of β-amino aldehydes generated by the competitive oxidation of the alcohol under TPAP/NMO conditions.

When compounds **10** and **11** with more substituents on the pyrrolidinemethanol fragment were subjected to $OsO_4$/NMO conditions with higher $OsO_4$ loading (6 mol%), 3,3,5-trisubstituted hexahydropyrrolo[2,1-*b*]-1,3-oxazole **12** and 4,4,6-trisubstituted hexahydro-2H-pyrrolo[2,1-*b*]-1,3-oxazine **13** were obtained in 83% and 84% yields, respectively. The reaction of **11** under TPAP/NMO conditions was complicated by the oxidation of the alcohol but still provided **13** in a moderate yield (53%). Notably, when two alkene-tethered cyclic amines **14a/b** were subjected to the $OsO_4$/NMO conditions, diastereospecific products **15a/b** were obtained in moderate yields, presumably as a result of the strong coordination in the $OsO_4$/NMO-mediated alkene dihydroxylation and oxidative cyclization (Scheme 3). The structures of **12**, **13** and **15a/b** were determined by 2D NOESY experiments (see the ESI), and the structure of **15b** was confirmed by X-ray crystallography, as shown in Figure 1.[13]




**Scheme 3.** Oxidative cyclizations of **10, 11,** and **14a/b**

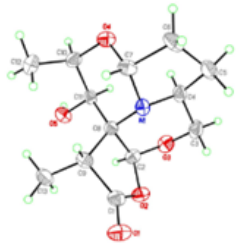
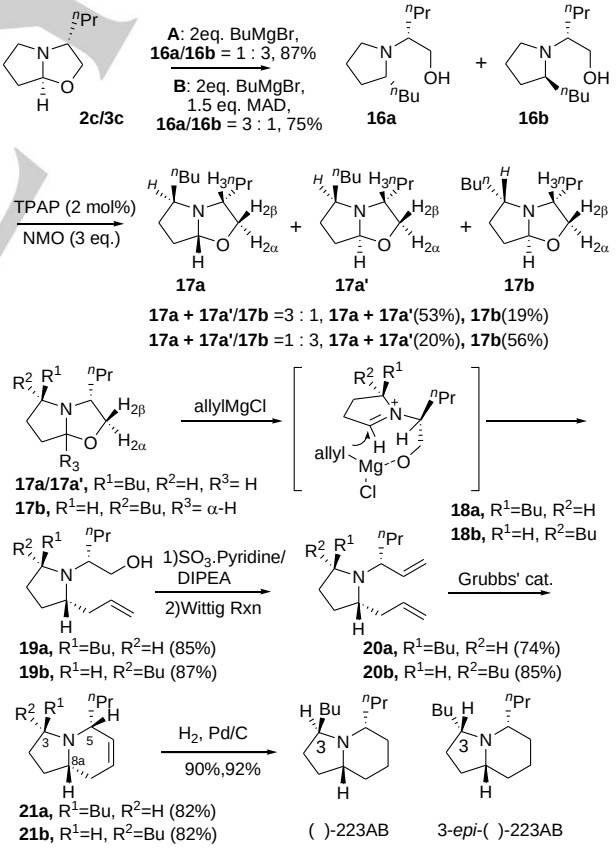


**Figure 1.** Structure of **15b** obtained by X-ray crystallography**.**




**Scheme 4.** Synthesis of (–)-223AB and 3-*epi*-(–)-223AB

The iterative C($sp^3$)-H activation of cyclic amines to afford the N,O-acetals by $Ag_2O$ following alkyl Grignard addition has been applied in the synthesis of α,α'-disubstituted cyclic amines.[14] We envisioned that the opening of aminal **2c/3c** by an alkyl Grignard following the second activation/Grignard addition can provide the 2,5-disubstituted pyrrolidine intermediate needed for the synthesis of 3,5-disubstituted indolizidine 223AB.[15,16,17] Therefore, the synthesis of 223AB and a related analogue commenced with the ring opening of **2c/3c** by an alkyl Grignard. Although the reaction with simple butyl Grignard afforded inseparable mixtures of **16a/b** (87%) in 1/3 ratio, the addition of methylaluminum bis(2,6-di-tert- butyl-4-methyl phenoxide (MAD) with the Grignard reagent reversed the preference and resulted in a 3/1 ratio (75%). The reactions of both mixtures of **16a/b** under TPAP/NMO conditions provided separable **17a/17a'** and **17b** in 20%/56% and 53%/19% yields, respectively. The structures of **17a** and **17b** were determined by 2D NOESY experiments (see the ESI). The reactions of **17a/17a'** and **17b** with allyl Grignard afforded **19a** (85%) and **19b** (87%) respectively with high diastereoselectivities. Iminium intermediates **18a/18b,** avoiding the $A^{1,3}$-strain, were proposed to account for the facial selectivity during the Grignard addition,[18] as this effect outweighed the steric effects involving the existing butyl group on the pyrrolidine ring. Ley-Griffith oxidation following the methylene olefination of **19a** and **19b** gave **20a** and **20b** in 74% and 85% yields, respectively. Ring-closing metathesis of dienes **20a** and **20b** gave **21a** and **21b** in 82% and 82% yields, respectively, and the final hydrogenation of **21a** and **21b** using palladium on carbon under a hydrogen atmosphere completed the synthesis of alkaloid (–)-223AB (90%, $[\alpha]^{30}_D$ –93.2 (*c* 0.5, MeOH), lit.[16o] $[\alpha]^{20}_D$ –85.0 (*c* 0.42, MeOH)) and 3-*epi*-(–)-223AB (92%, $[\alpha]^{28}_D$ –13.2 (*c* 0.2, MeOH), lit.[17b] $[\alpha]^{23}_D$ –11.1 (*c* 0.2, MeOH)). The NMR data of synthetic indolizidines (–)-223AB and 3-*epi*-(–)-223AB were consistent with the reported data (Scheme 4).

In summary, we report here the general oxidative cyclization of amino alcohols with $OsO_4$/NMO or TPAP/NMO conditions to afford cyclic N,O-acetal compounds in moderate to good yields. The most obvious benefit of these two reactions is to functionalize the carbon neighboring the nitrogen and to protect the latent functionality in one step. A tandem dihydroxylation/oxidative cyclization reaction was discovered when an alkene-substituted cyclic amine was subjected to the $OsO_4$/NMO reaction conditions. Finally, the synthetic potential of these two transformations was demonstrated via sequential oxidative cyclization/Grignard addition reactions in the protecting group-free synthesis of indolizidines (–)-223AB and 3-*epi*-(–)-223AB.

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**Keywords:** asymmetric catalysis, C-H functionalization, oxidative cyclization, osmium tetroxide, TPAP.

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[13] CCDC 1941078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/

structures.

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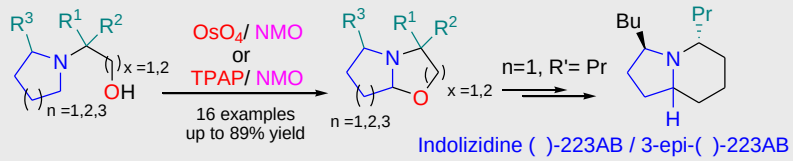
# COMMUNICATION




Efficient protocols for the oxidative cyclizations of amino alcohols by two of the platinum group metal oxides, namely osmium tetroxide and tetrapropylammonium perruthenate with NMO, were found to provide N,O-acetal moieties by trapping the resulting iminium ion with the alcohol. These two transformations were demonstrated in the protecting group-free synthesis of poison-dart frog indolizidines (–)-223AB and 3-*epi*-(–)-223AB.

C-H Functionalization

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**C-H Functionalization of Amino Alcohols by Osmium Tetroxide/NMO or TPAP/NMO: Protecting Group-Free Synthesis of Indolizidines (–)-223AB and 3-*epi*-(–)-223AB**