Title

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Cyclic Osmate Esters from 1,2- and 1,3-Diols and α-Hydroxy Acids for X-ray Analysis

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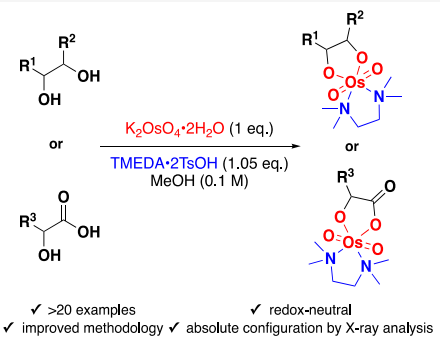
ABSTRACT: We previously demonstrated that osmium tetroxide and TMEDA generate stable crystalline adducts with alkenes that facilitate X-ray analysis and structure assignments. Alternatively, osmate esters can be prepared from diols, potassium osmate, and TMEDA·2TsOH in a nonoxidative condensation reaction. This new approach provides a convenient route to form stable, crystalline osmate(VI) esters for X-ray analysis. Because it is redox neutral, it works with a variety of diol substrates, including 1,3-diols, that cannot be prepared from alkenes. α-Hydroxy acids also form stable osmate esters in reasonable yields and readily crystallize. An alternative ligand screen was performed to assess the improved crystallinity from substituted TMEDA analogues. The enhanced crystallinity of osmate esters and the incorporation of a heavy atom make a reliable determination of structure and absolute configuration routine.



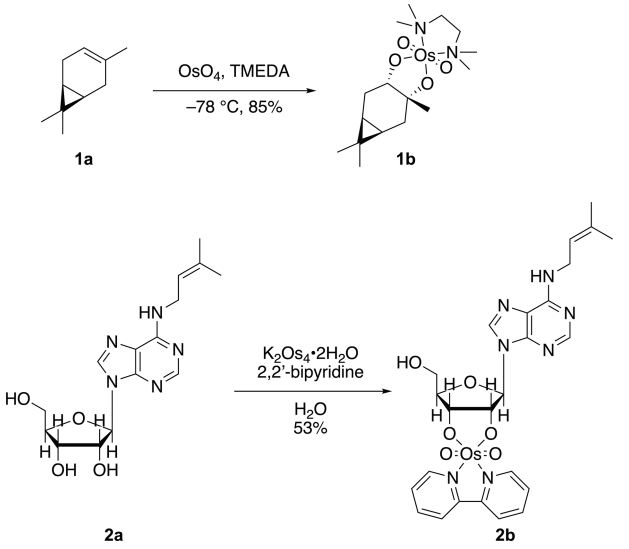
INTRODUCTION

Donohoe reported that OsO_4 and TMEDA formed a very reactive complex that led to hydroxyl-directed osmylation of alkenes.[1] The resulting osmate esters were remarkably stable, and several were analyzed by crystallography. We reported that this osmylation reaction could be repurposed for structure analysis by generating crystalline derivatives suitable for X-ray determination (Scheme 1A).[2] Several other groups have since applied this strategy for determining the structure of a variety of complex alkenes.[3]

One important limitation of this approach was found when the osmylation reaction was not stereoselective and generated mixtures of diastereomers.[2] In some cases, the diastereomers could be separated by chromatography and analyzed, but in other cases, they could not be separated, and X-ray analysis was not possible. A problematic example was found in the osmylation of lanosterol (Scheme 2), which led to an inseparable 1:1 mixture of diastereomers. The diastereomers could not be separated, and X-ray analysis failed.

Considering alternatives to remove this limitation, an enantioselective reaction with a chiral derivative of TMEDA was considered to improve the diastereoselective of the osmylation, but these stoichiometric osmylation reactions had been extensively studied in the past, and the necessary chiral amines were structurally complex and difficult to prepare. However, the Sharpless asymmetric dihydroxylation (SAD) is a wonderful solution for catalytic, enantioselective osmylation of a very wide variety of alkenes.[4] If we combined diastereomerically enriched diols from SAD with osmium(VI) reagents, then it could provide a convenient method to

Scheme 1. (A) Our Previous Work on the Absolute Structure Assignments of Alkenes[2]; (B) Ragazzo and Behrman's Regioselective Osmylation of Isopentyl Adenosine[5]



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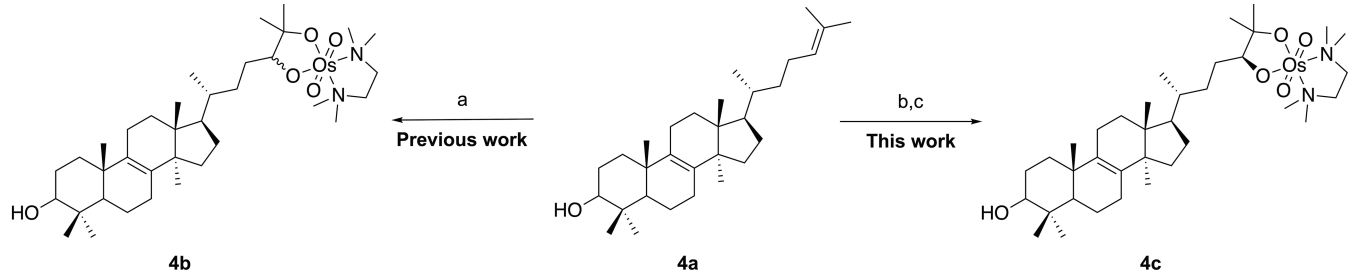
Scheme 2. Reagents and Conditions: (a) OsO_4, TMEDA, −78 °C, 1:1 dr, (b) $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, $(DHQD)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, EtOAc, *t*-BuOH/H_2O, 0 °C, 6 h, 33%, (c) $K_2OsO_4{\cdot}2H_2O$, TMEDA·2TsOH, MeOH, rt, 16 h, 22%



overcome the problem and extend the utility of the osmate ester crystallization strategy. This approach is described below.

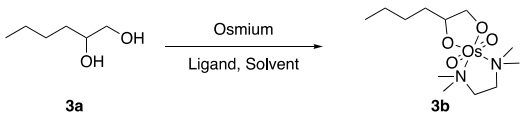
The new methodology described herein is the redox neutral generation of cyclic osmate esters from diols. This approach has precedent from the work of Ragazzo and Behrman, who found that potassium osmate and bipyridine in water formed a cyclic osmate derivative from an 1,2-diol (Scheme 1B).[5] While Behrman's work was reported and used to study an adenine derivative, we are not aware of any osmate diol complexes used to generate crystals for X-ray crystals. Our method uses potassium osmate, a safe osmium(VI) salt, and TMEDA to generate cyclic osmate-TMEDA esters of diols. The TMEDA complexes were stable to standard workup conditions and chromatography on silica gel. The osmate ester formation does not begin with alkenes, so a much wider variety of diols and related functional groups can be incorporated. Most of the osmate TMEDA esters were crystalline, and many were analyzed by X-ray crystallography.

Diols are common functional groups in natural products but do not often lend themselves to crystallization. The structure analysis of complex diols and polyols usually focuses on NMR analysis,[6] but it would benefit greatly from a reliable method for generating crystalline derivatives. There are common derivatization methods for alcohols that can be helpful with diols, such as the preparation of *p*-bromobenzoate esters[7] or ferrocene carboxylate esters,[8] but they have a mixed record of success for inducing crystallinity. Derivatization of alcohols as sulfate esters and forming crystals with guanidinium cations is a fascinating approach, but it has not yet been applied to diols.[9]

RESULTS AND DISCUSSION

We began our studies by optimizing reaction conditions to form osmate TMEDA complexes using 1,2-hexanediol **3a**, as presented in Table 1.[10] The initial conditions used osmium tetroxide and TMEDA with the addition of triphenylphosphine to reduce the metal to the correct oxidation state (entry 1). Using various temperatures and procedural changes, these conditions consistently led to incomplete conversion to desired osmate ester **3b**. Following precedent from Behrman, we decided to attempt using potassium osmate while keeping TMEDA as the ligand. This reaction led to the formation of the osmate ester, but incomplete conversion resulting in 43% yield that was comparable to the previous results obtained (entry 2). Changing the solvent to dichloromethane and increasing the temperature to 40 °C (entry 3) led once again to 43% isolated yield of the product. In the Behrman precedent (Scheme 1B), the reaction mixture was brought to pH 7 by the addition of 1 M aq. HCl. Mimicking this approach, the TMEDA was added as a protonated salt to achieve approximately neutral pH. When TMEDA·2TsOH was used in methanol (entry 4), the osmate **3b** was isolated in 84% yield. Extending the reaction time from 1 to 16 h slightly increases the yield to 90%. Entry 5 represents the optimized conditions for osmate TMEDA ester formation from diols.

Table 1. Reaction Optimization of Cyclic Osmate Ester Formation Using 1,2-Hexanediol[a]



entry	osmium	ligand	time	yield
1[b]	OsO_4	TMEDA (1.0)/PPh_3 (1.0)	5 h	40%
2	$K_2OsO_4{\cdot}2H_2O$	TMEDA (3.0)	2 h	43%
3[c]	$K_2OsO_4{\cdot}2H_2O$	TMEDA (1.1)	2 h	43%
4	$K_2OsO_4{\cdot}2H_2O$	TMEDA·2TsOH (1.05)	1 h	84%
5	$K_2OsO_4{\cdot}2H_2O$	TMEDA·2TsOH (1.05)	16 h	90%

[a]Standard conditions: 1.0 equiv diol in 0.1 M MeOH at room temperature. [b]Reaction was performed neat at −40 °C and was warmed to room temperature. [c]Reaction was performed in CH_2Cl_2 at 40 °C.

With optimized conditions for a 1,2-diol, we returned to the problem of lanosterol (Scheme 2). Sharpless asymmetric dihydroxylation of lanosterol generated a stereodefined 1,2-diol. Treatment of the diol with potassium osmate and TMEDA·2TsOH under the optimized conditions (Table 1) afforded the desired osmate ester as a pure diastereomer (and enantiomer). Purification and crystallization gave crystals of **4c** suitable for X-ray analysis, and the resulting structure is shown in Figure 1.

Following the successful crystallization of the lanosterol derivative, we extended this strategy to a variety of diols. The results are presented in Table 2. We began with simple substrates, including *cis*-1,2-cyclohexanediol (**5a**) and *trans*-1,2-cyclohexanediol (**6a**). Compounds 5a and **6a** both formed Os(VI) esters in good yields under standard conditions, with the *trans*-configuration slightly more efficient. Formation of the *trans* ester **6a** was encouraging as the long osmium−oxygen bonds (1.958 and 1.966 Å) accommodated the normally strained geometry of the 5,6-*trans*-fused system. The osmate esters of glycerin (**7a**), (*R*)-4-(benzyloxy)butane-1,2-diol (**8a**), and ethyl (3*R*)-2,3-dihydroxy-3-phenylpropanoate (**9a**) readily crystallized after purification in excellent yields. Conversely,

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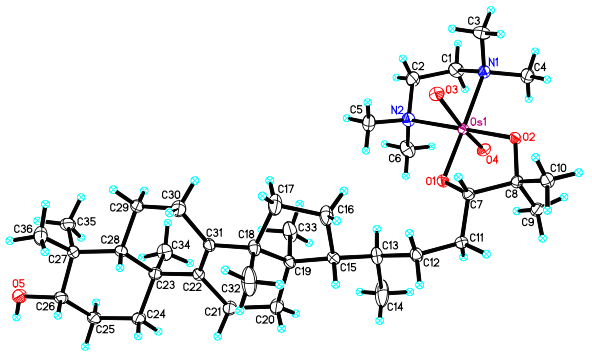


Figure 1. X-ray structure of **4c**. Two molecules of the formula unit were present in the unit cell, with one omitted for visual simplicity.

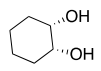
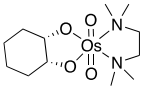
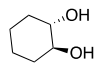
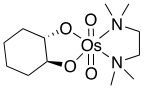
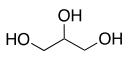
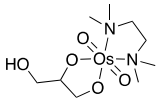
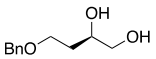
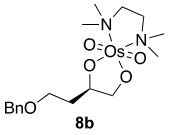
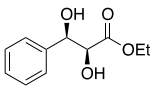
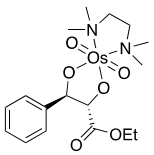
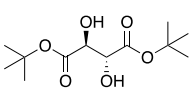
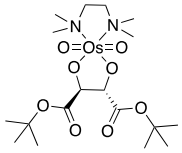
the osmylation of (+)-di-*tert*-butyl L-tartrate (**10a**) proceeded with a moderate yield due to incomplete conversion. A synthetic intermediate **11a** was tested, and complexation was successful in good yield. Lastly, a derivative of vitamin C (often termed a sugar acid) (**12a**) was analyzed and successfully osmylated and crystallized on the first attempt. This is a promising result as it can be difficult to obtain crystal structures of sugars. Several traditional sugars were later attempted; however, multiple free alcohols tended to result in various products that affected crystallization results.

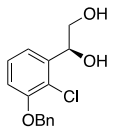
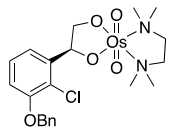
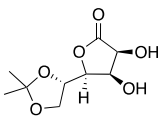
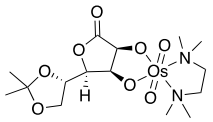
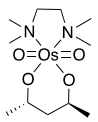
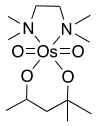
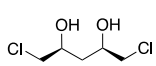
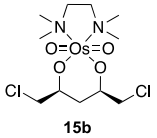
We next sought to expand the substrate scope to 1,3-diols. There was little precedent for the formation of a 1,3-diol osmate ester. Behrman noted that 1,2-diols outcompete 1,3-diols in transesterification reactions with nucleosides.[3] The only example of a 1,3-diol osmate ester was from Paquette's approach to functionalized taxanes, wherein dihydroxylation of an allylic alcohol intermediate with OsO_4/pyridine led to the stable osmate ester.[11] This triol osmate ester is interesting but not applicable to other 1,3-diols.

Diol **13a** was evaluated with our optimized conditions (Table 1, entry 5) that led to a 62% yield of osmate ester (**13b**). This osmate ester crystallized on the first attempt, allowing us to attain the first X-ray structure of a 1,3-diol osmate ester. 2-Methyl-2,4-pentanediol (**14a**) was then reacted under standard conditions to give the osmate **14b** in 45% yield, accompanied by recovered starting material. Similarly, diol **15a** gave osmate ester **15b**, but in modest yield. All of the compounds reported in Table 2 were crystallized and successfully evaluated by X-ray diffraction.

Attempts to improve osmate ester formation from 1,3-diols were largely unsuccessful. Aprotic solvents, such as DCE, CH_2Cl_2, 1,4-dioxane, and MeCN, were investigated at room temperature and at reflux to prevent exchange of a protic

Table 2. Diols and the Derived Crystalline Osmate−TMEDA Esters[a]

Diol	Yield	Osmate	mp
 **5a**	70%	 **5b**	134–140 °C (dec)
 **6a**	95%	 **6b**	65–66 °C
 **7a**	98%	 **7b**	134–142 °C (dec)
 **8a**	80%	 **8b**	102–108 °C (dec)
 **9a**	93%	 **9b**	64–66 °C
 **10a**	41%	 **10b**	148–152 °C (dec)

Diol	Yield	Osmate	mp
 **11a**	68%	 **11b**	198–204 °C
 **12a**	73%	 **12b**	152–156 °C
 **13a**	62%	 **13b**	150–152 °C (dec)
 **14a**	45%	 **14b**	180–184° C
 **15a**	21%	 **15b**	120–134 °C

[a]Standard conditions: 1.0 equiv diol and 1.05 equiv TMEDA·2TsOH, MeOH, rt, then add 1.0 equiv $K_2OsO_4·2H_2O$, 16 h.

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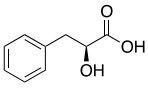
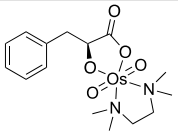
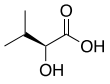
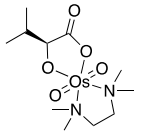
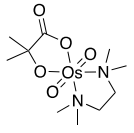
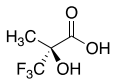
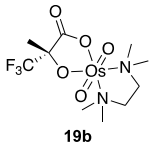
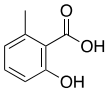
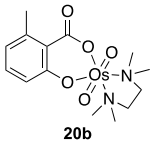
solvent with the osmium; however, this led to poor solubility within the reaction mixtures. Protic solvents, such as HFIP, H_2O, TFE, and IPA, at room and elevated temperatures tended to result in no reaction or undesired products that significantly decreased the reaction yields while still resulting in incomplete conversion of starting material. Doubling the equivalence of $K_2OsO_4{\cdot}2H_2O$ and TMEDA·2TsOH, overnight complexation of TMEDA and TsOH, anhydrous conditions, premixing of the diol and $K_2OsO_4{\cdot}2H_2O$ then charging in TMEDA·2TsOH, and similar efforts all resulted in incomplete conversion of 1,3-diol starting material.

Several other bidentate structures were evaluated under standard conditions to find new cyclic osmate(VI) structures. The most promising ones were α-hydroxy acids. The results are included in Table 3. The α-hydroxy acids formed cyclic

Table 3. Hydroxy Acids and the Derived Crystalline Osmate−TMEDA Esters[a]

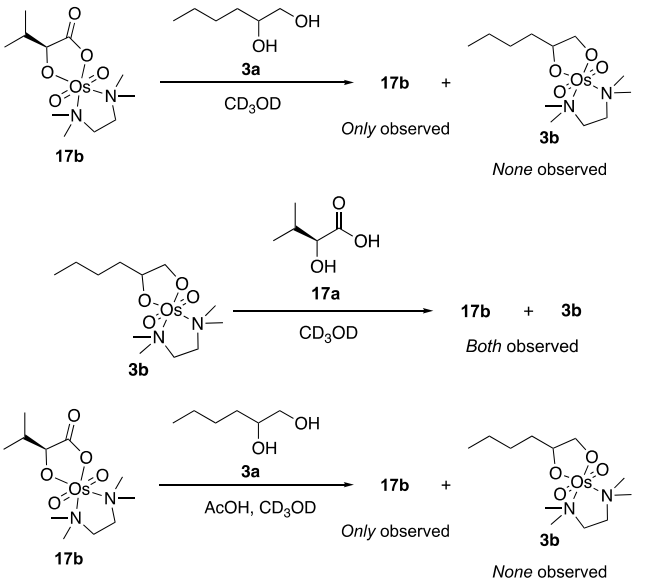
Acid	Yield	Osmate	mp
 16a	60%	 16b	146–154 °C (dec)
 17a	77%	 17b	67.1–68.5 °C
 18a	67%	 18b	194.0–196.0 °C
 19a	56%	 19b	200–245 °C (dec)
 20a	17%	 20b	59.0–61.0 °C

[a]Standard conditions: 1.0 equiv diol and 1.05 equiv TMEDA·2TsOH, MeOH, rt, then add 1.0 equiv $K_2OsO_4{\cdot}2H_2O$, 16 h.

osmate esters very readily and in reasonable yields. They formed crystals easily, and X-ray structures were solved in all cases. These types of complexes have been reported before, and there is at least one crystal structure of an α-hydroxy ester Os(VI) complex.[12] These TMEDA complexes all showed good stability and were purified by chromatography. The salicylic acid derivative **20a** led to a cyclic osmate ester, but in modest yield. Attempts to generate complexes from other β-hydroxy acids were unsuccessful; therefore, complex **20b** is an anomalous outcome. Although α-hydroxy acids are more often crystalline materials than diols, the cyclic osmate esters may be useful for X-ray structure analysis.

It was not clear to us whether the diol osmate complexes were kinetically stable. We investigated equilibration using diol complex **3b** and α-hydroxy acid complex **17b** (Scheme 3).

Scheme 3. (A) Attempted Equilibration Reaction between the Osmate Ester of an α-Hydroxy Acid (17b) and 1,2-Hexanediol (3a); (B) Reverse Equilibration Reaction between the Osmate Ester of 1,2-Hexanediol (3b) and (*S*)-2-Hydroxy-3-methylbutanoic Acid (17a); (C) Attempted Equilibration Reaction between the Osmate Ester of an α-Hydroxy Acid (17b) and 1,2-Hexanediol (3a) with Acetic Acid



Combining **17b** with diol **3a** did not lead to any exchanged as observed by NMR spectroscopy (Scheme 3A). On the other hand, diol complex **3b** did exchange slowly with hydroxy acid **17a** but did not exchange completely (Scheme 3B). We expected these experiments to head toward a similar equilibrium point, but this outcome was not observed. The addition of acetic acid (as a potential catalyst) did not change the outcome (Scheme S1). We suspect that there may be other osmate species in solution, rendering the exchange process more complex than initially hypothesized. Our tentative conclusion is that exchanges are possible but may be relatively slow and unimportant under the standard complexation conditions.

Amino acid derivatives were also evaluated for osmate ester formation. There has been at least one reported crystal structure in the literature of an osmium(VI)-amino acid complex and other studies on general reactivity for tissue fixation and staining using osmium tetraoxide.[13] Using our method, unprotected amino acids, such as L-proline or D-(−)-alpha-phenylglycine, did not form osmate complexes. However, Boc-protected phenylalanine did form a complex (**21**) in 70% yield under the standard conditions. On X-ray analysis, we were surprised to find that carboxylate alone coordinated with the osmium atom; the other ligand was water rather than the carbamate. The structure is shown in Figure 2. Amino acid derivatives were not found to effectively form cyclic osmate esters

Stable osmate esters were formed from several diols, but the complexes did not crystallize. Three examples are listed in

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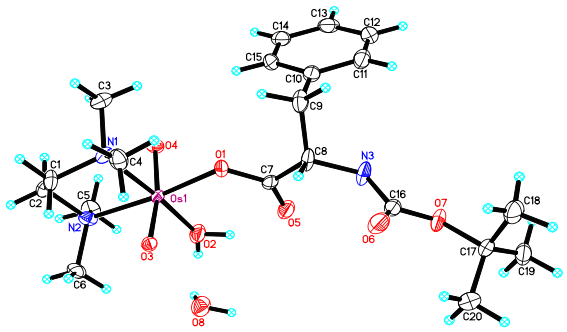
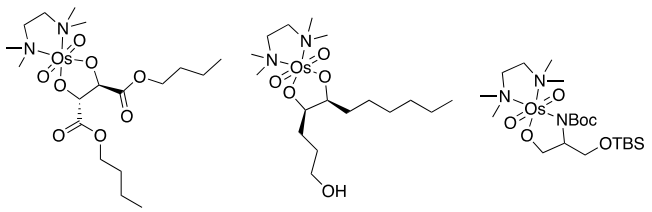


Figure 2. Solved Boc-Phe-OH (**21**) TMEDA complex.

Figure 3. Complexes **22** and **23** both contain aliphatic chains that lower the crystallinity. The N-Boc amino alcohol **24** also



78% yield **22** 81% yield **23** 57% yield **24**

Figure 3. Cases of successful complexation but unsuccessful crystallization.

formed a complex that resisted crystallization. Given the surprising result with the N-Boc amino acid, the structure of the material in the absence of crystallographic data is unclear.

In response to several osmate esters successfully complexing but not crystallizing, we explored TMEDA alternatives to assess the enhancement of crystallinity. We explored model substrates shown in Table 4 using (1*R*,2*R*)-tetramethylcyclohexane-1,2-diamine and (1*R*,2*R*)-tetramethyl-1,2-diphenylethane-1,2-diamine as alternative ligand sources. Using 1,2-hexanediol as a model substrate, we were able to obtain crystalline solids; however, due to the greasy nature of the product that was displayed in Figure 3, the quality of the crystals was not high enough for absolute determination through X-ray analysis with all ligands attempted (**3b**, **25**, and **26**). The latter two cases also involve mixtures of diastereomers that result from an enantiopure diamine and a racemic diol. Using (*R*)-propane-1,2-diol and glycerol as test substrates minimized the diastereomer problem, and X-ray analysis was successful for all substrate–ligand pairs. (1*R*,2*R*)-Tetramethylcyclohexane-1,2-diamine displayed higher melting points than TMEDA complexed osmate esters; however, (1*R*,2*R*)-tetramethyl-1,2-diphenylethane-1,2-diamine was shown to be the most promising alternative ligand with the highest observed crystallinity.

CONCLUSIONS

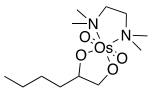
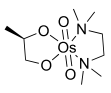
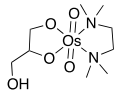
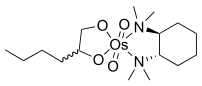
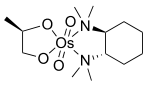
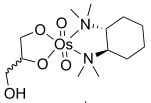
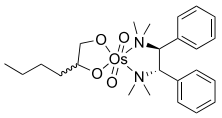
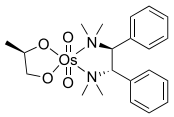
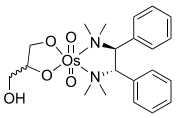
In conclusion, a nonoxidative method for the formation of osmate esters from 1,2- and 1,3-diols, as well as α-hydroxy acids for X-ray analysis, has been described. The method is simple and allows for the formation of crystalline derivatives. In some cases, alternatives to TMEDA led to more highly crystalline derivatives. This approach should be useful in organic structure assignments.

EXPERIMENTAL SECTION

General Procedure for TMEDA·2TsOH (S1b). To a solution of TMEDA (0.218 g, 1.88 mmol) in acetone (9.4 mL) was added TsOH·H_2O (0.713 g, 3.75 mmol), and the mixture was stirred at ambient temperature. After 1 h, a white precipitate had formed. The mixture was cooled to 0 °C, and the solution was filtered through a sintered glass funnel. The solid was collected and dried in vacuo, affording **S1b** (0.795 g, 92%) as a white solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.72 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 3.63 (s, 2H), 2.97 (s, 7H), 2.38 (s, 3H). ^{13}C{1H} NMR (151 MHz, CDCl3) δ: 143.2, 142.0, 130.0, 126.9, 52.5, 44.3, 21.3.

General Procedure for (1*R*,2*R*)-Tetramethyl-1,2-diphenylethane-1,2-diamine (S3b). General procedure for (1*R*,2*R*)-tetramethyl-1,2-diphenylethane-1,2-diamine was synthesized according to a modified literature procedure.[14] To (1*S*,2*S*)-1,2-diphenylethylenedi-amine (1.26 g, 4.99 mmol) was added formic acid 90% (3.8 mL) and a 37% aq. solution of formaldehyde (5.0 mL). The solution was heated to reflux and stirred for 1 day. 2 M HCl (2.5 mL) was then added to the stirring reaction mixture, and the reaction was allowed to

Table 4. Select Diamine Ligand Screening

Osmate	Yield	mp	Osmate	Yield	mp	Osmate	Yield	mp
 **3b**[a]	90%	74–76 °C	 **27**[a]	26%	75–80 °C	 **7b**[a]	98%	134–142 °C (dec)
 **25**[b]	65% 1:1	N/A[d]	 **28**[b]	43%	116 °C (dec)	 **30**[b]	24% 1:1	158–164 °C (dec)
 **26**[c]	100% 1:1	164–166 °C	 **29**[c]	60%	160 °C (dec)	 **31**[c]	76% 1:1	162–168 °C (dec)

[a]Standard conditions: diol, $K_2OsO_4·2H_2O$, TMEDA·2TsOH, MeOH, rt, 16 h. [b]Standard conditions: diol, $K_2OsO_4·2H_2O$, (1*S*,2*S*)-tetramethylcyclohexane-1,2-diamine (**S2b**), TsOH·H_2O, MeOH, rt, 16 h. [c]Standard conditions: diol, $K_2OsO_4·2H_2O$, (1*R*,2*R*)-tetramethyl-1,2-diphenylethane-1,2-diamine (**S3b**), TsOH·H_2O, MeOH, rt, 16 h. [d]Crystallization attempts were unsuccessful and no melting point could be obtained.

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react for 2 additional days at 100 °C. The solution was then concentrated via an air stream. Ether (10 mL) was then added, followed by cooling in an ice bath and addition of 6 M NaOH (~10 mL) until the solution was neutral. The solution was then extracted with ether (3 × 30 mL), and the organic layer was washed with brine (1 × 30 mL). The combined organic layers were then dried with Na_2SO_4 and concentrated in vacuo. Product **S3b** was then filtered in boiling heptane and azeotroped with pentane to give a colorless solid (851 mg, 67%) that matches literature reported spectral data.[14] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (t, J = 7.6 Hz, 4H), 7.04 (td, J = 7.2, 1.4 Hz, 2H), 7.00−6.98 (m, 4H), 4.24 (s, 2H), 2.25 (s, 12H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ: 133.93, 130.02, 127.35, 126.68, 67.96, 40.92.

General Procedure for TMEDA Complexed Osmate Ester Formation. To a stirred solution of diol, hydroxy acid, amino acid, or amino alcohol (0.0446 mmol, 1.0 equiv) in methanol (0.7 mL, 0.1 M) was added TMEDA·2TsOH (0.0468 mmol, 1.05 equiv). Potassium osmate (0.0446 mmol, 1.0 equiv) was then added, and the reaction mixture was stirred at ambient temperature. The reaction was monitored by TLC, as well as the solubilization of the potassium osmate. When the reaction was complete, the mixture was filtered through a pad of Celite and the filtrate was evaporated. The crude material was purified by flash chromatography (0−20% MeOH in CH_2Cl_2) to yield the brown osmate ester.

General Procedure for (1*R*,2*R*)-Tetramethyl-1,2-diphenylethane-1,2-diamine Complexed Osmate Ester Formation. To a stirred solution of diol (0.108 mmol, 1 equiv) in methanol (1.1 mL, 0.1 M) were added TsOH·H_2O (0.217 mmol, 2 equiv) and (1*R*,2*R*)-tetramethylcyclohexane-1,2-diamine (**S2b**) or (1*R*,2*R*)-tetramethyl-1,2-diphenylethane-1,2-diamine (**S3b**) (0.114 mmol, 1.05 equiv). Potassium osmate (0.108 mmol, 1.0 equiv) was then added, and the reaction mixture was stirred at ambient temperature. The reaction was monitored by TLC, as well as observing the solubilization of the potassium osmate. When the reaction was complete, the mixture was filtered through a pad of Celite, and the filtrate was evaporated. The crude material was purified by flash chromatography (0−20% MeOH in CH_2Cl_2) to yield the brown or black osmate ester.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c03119.

Experimental procedures; mechanistic investigations; full characterization including ^{1}H NMR, ^{13}C NMR, Rf, and HRMS data for all products; and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2408128, 2408130−2408140, 2410345−2410352 and 2420816 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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