Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media: Old Process, New Tricks

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Abstract: A screen of over 500 diversely functionalized additives in osmium-catalyzed dihydroxylation has uncovered that electron-deficient olefins are converted into the corresponding diols much more efficiently when the pH of the reaction medium is maintained on the acidic side. Further studies have identified citric acid as the additive of choice, for it allows preparation of very pure diols in yields generally exceeding 90%. As described here, a much wider range of olefin classes can now be successfully dihydroxylated. The process is experimentally simple, in most cases involving little more than dissolving the reactants in water or a water/*tert*-butyl alcohol mixture, stirring them, and filtering off the pure diol product.

Keywords: alkenes; dihydroxylations; homogeneous catalysis; osmium; oxidations

Introduction

Addition of osmium tetroxide to olefins[1] is probably the most selective and reliable organic transformation for two simple reasons: 1) OsO_4 reacts with *virtually all* olefins, and 2) it reacts slowly, if at all, with the other common organic functional groups. Its catalytic asymmetric version, the AD reaction, known for its broad scope, has become a widely utilized procedure for enantioselective introduction of the vicinal diol moiety.[2] Various stoichiometric reagents have been utilized for the Os(VI) → Os(VIII) reoxidation step in the catalytic cycle. Three were found to be particularly effective, *tert*-butyl hydroperoxide (TBHP),[3] 4-methylmorpholine *N*-oxide (NMO, the Upjohn process),[4] and potassium ferricyanide (used as reoxidant in AD-mixes).[5] Note that all of these osmium-catalyzed processes are performed under neutral to basic conditions, and although a wide range of variously substituted olefins can now be successfully dihydroxylated, certain substrate classes still present problems. The latter appear to arise from low catalyst turnover numbers, overoxidation and, as a consequence, low yield and purity of the products. For example, α,β-unsaturated amides react sluggishly, requiring long reaction times and high catalyst loadings to achieve good yields and reasonable reaction times.[6] Sterically encumbered and/or tetrasubstituted olefins usually exhibit both very poor turnover rates and enantioselectivities.

Discovery and General Aspects

We have recently developed a high-throughput, mass spectrometry-based analytical method for screening the effect of reaction variables, in particular additives, on catalytic transformations.[7] Modern robotics equipment, which can dramatically accelerate routine tasks of weighing, dissolution, addition, and sampling,[8] has allowed us to screen a large number of differently functionalized organic additives for their effects on the dihydroxylation process. An α,β-unsaturated amide was selected as standard substrate in the screen. In the preliminary study, NMO was used as the stoichiometric oxidant and low catalyst loadings (0.1 mol % OsO_4) were employed to favor high sensitivity of the catalysis to any effects of the additives. Screening of over 500 compounds containing diverse functionalities led to a surprisingly simple conclusion: *product yields were markedly improved when additives bearing acidic functional groups were present*. Furthermore, additives with basic functionalities inhibited the turnover, measured as the yield of the diol **2** (Figure 1).

Clearly, this unknown pH phenomenon merited more detailed examination. To this end, many dihydroxylations of *trans-N,N*-dimethylcinnamamide (**1**) with controlled concentrations of various acidic additives were conducted. The progress of reactions was monitored using ESI-MS analysis to measure the yield of the diol (**2**) formed.[9] The control reaction, which was run in the absence of any additives, stalled at ca. 50% conversion.

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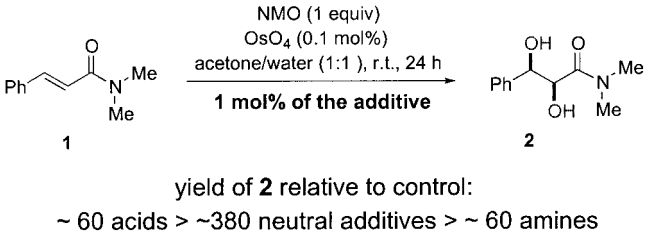


Figure 1. Effect of additives on diol yields.

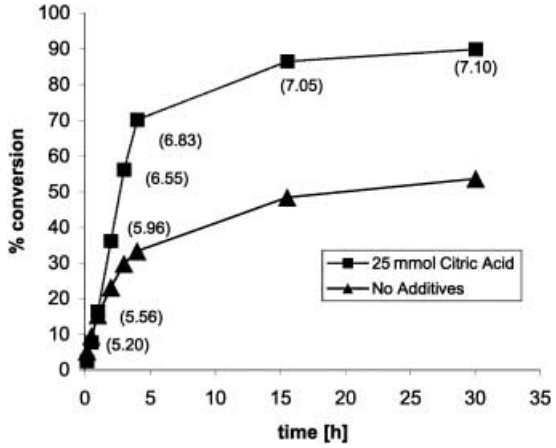


Figure 2. Reaction rate profile for the dihydroxylation of *trans-N,N*-dimethylcinnamamide (**1**); conditions: acetone/water 1:1 (0.1 M in olefin), 1 equiv. NMO, 0.1 mol % OsO_4, r.t.; the numbers in parentheses indicate pH values during the course of the reaction.

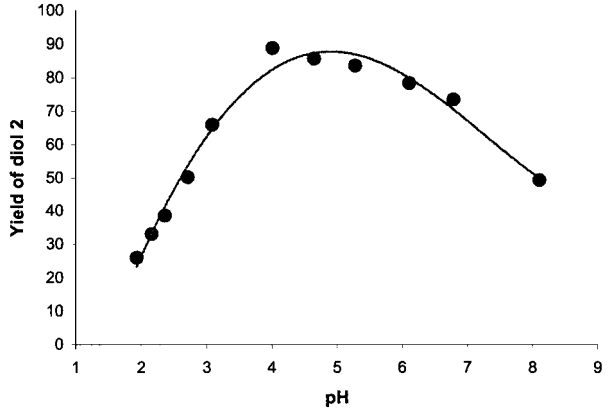
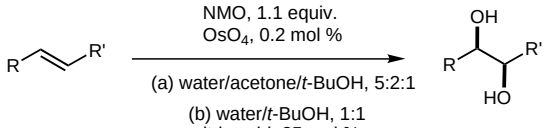
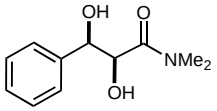
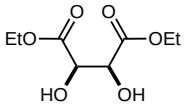
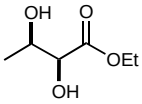
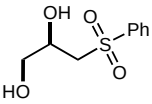
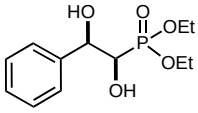


Figure 3. Dependence of the yield of the diol (**2**) on pH (sulfuric acid was used to lower the pH).

The pH of this system remained throughout in the 8 to 9 range. However, yields were improved to over 90% when reaction mixtures were acidified to bring the initial pH to the optimal range of 4 to 6 (Figures 2 and 3). Figure 2 also reveals that a substantial increase in the pH (ca. 2 units) occurs during the course of the reaction.

Table 1. Dihydroxylation of electron-deficient olefins under (a) "standard" versus (b) new, "acidic" conditions.



Entry	Product	Yield [%] (a) standard conditions	Yield [%] (b) new conditions
1		50	96
2		<10	76
3		45	67
4		<40	78
5		30	77

To probe the scope of this novel process, a series of dihydroxylations with 25 mol % citric acid as the additive were performed. All reactions were run 0.5 M in olefin. The improvements achieved are best appreciated through the results shown in Table 1. A variety of olefins bearing electron-withdrawing functionality, such as amides, esters, sulfones and phosphonates, benefit most from added citric acid (Table 1).[10] Moreover, the diol products exhibited unexpected levels of purity. In every case the analytically pure and *colorless*[11] diol was isolated after a simple extractive work-up.

Mechanistic Considerations

The so-called "Upjohn process" for dihydroxylation of olefins with NMO, acetone, water, and catalytic osmium was discovered about fifty years ago by process research chemists at Upjohn. It first appeared in the open literature in 1976,[4] and soon became one of the top ten most used organic processes. Finding that this venerable reaction exhibits a dramatic, albeit unknown,

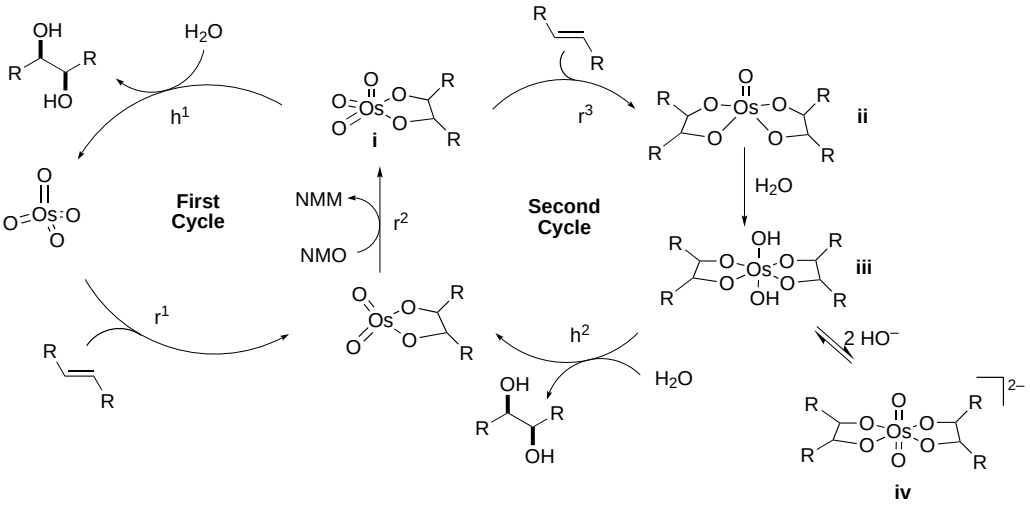


Figure 4. Proposed mechanism for the Os(VIII)-catalyzed dihydroxylation of olefins with NMO as reoxidant.

pH dependence naturally begs the question of the mechanistic origin of the phenomenon.

After screening a number of substrates containing acidic functionalities, α-hydroxycarboxylic acids (e.g., hydroxyacetic, malic, tartaric, and citric) proved most effective. Within this class, citric acid is unique: its use ensures both the highest yield and the highest purity of the product diol. We believe its role to be two-fold. First, it neutralizes 4-methylmorpholine formed in the course of the reaction and maintains the pH in the optimal range. Second, it acts as a ligand for osmium, keeping the active Os(VI) form of the catalytic species in solution by stabilizing it against disproportionation to Os(VIII) and insoluble Os(IV) species. The latter, beyond being permanently shut out from participation in the desired catalysis, seem to bind aggressively to the diol product thereby further contaminating it. Our current understanding of these two effects is described below.

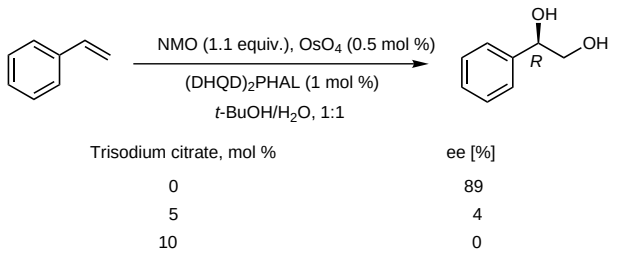
One particularly helpful mechanistic insight arose during process improvement efforts with the catalytic AD system toward the end of the 1980′s. It was the discovery that *osmium-catalyzed dihydroxylation of olefins has the potential for proceeding via two fundamentally different catalytic cycles, and that in either cycle the rate-limiting step is glycolate hydrolysis either osmium monoglycolate **i** or bisglycolate **ii*** in Figure 4.[12] Under homogeneous conditions, where the reoxidant has constant access to all the catalytic intermediates, *the turnover is locked into the second cycle*. The hydrolysis of the bis(glycolate) **ii** is initiated by addition of a water molecule to this species, forming a putative intermediate **iii**. We propose that acids assist catalyst turnover in dihydroxylation by preventing the formation of the catalytically inert dioxoosmate dianion species **iv**, which arises from deprotonation of the hydrated bis(glycolate) **iii** at a higher pH.[13]

Based on this hypothesis, we prepared and tested the catalytic activity of both the green, neutral bis(glycolate) **ii** and the reddish dioxoosmate **iv** complexes of the diol **2**.[14] As an 18-electron complex, the latter is expected to be particularly stable and resistant to substitutions under basic conditions. Indeed, **iv** was found to be hydrolytically inert regardless of whether NMO is present or absent. The observation that all reaction mixtures under acidic conditions remain green, whereas under basic conditions they turn brown, is nicely consistent with the central tenants of the present hypothesis. It is noteworthy that olefins such as diethyl maleate show the greatest benefit from performing the dihydroxylation at lower pH. The hydrated osmium(VI) bis(glycolates) **iii** formed from such electron-poor olefins would be expected to be much more acidic and correspondingly more likely to get "locked up" as dianion **iv**, even in the presence of a relatively weak base, like 4-methylmorpholine.

If this simple acidic buffer hypothesis were the entire story, then many acids should suffice, provided the pH does not fall too low.[15] Indeed, we found that many other acids, including acetic, malic, tartaric, phosphoric, and sulfuric, accelerate these dihydroxylations. However, only citric acid provides *consistently high yields of outstandingly pure diols* from all olefins that respond favorably to dihydroxylation under acidic conditions. We believe the uniqueness of citric acid stems from its ability to chelate the osmium(VI) catalytic species [likely forming complexes like **v** (Figure 6)] and protecting it from the disproportionation known to occur under acidic conditions. Similar osmium(VI) complexes with other carboxylates have been described in the literature.[16]

In support of this idea, we found that added sodium citrate had a marked effect on the level of enantioselectivity achieved in asymmetric dihydroxylations of styrene (Figure 5).

In the absence of any additives, the *R*-configured diol product (89% ee) is obtained. However, the inherent,



Trisodium citrate, mol %	ee [%]
0	89
5	4
10	0

Figure 5. Effect of sodium citrate on enantioselectivity of asymmetric dihydroxylation (AD) of styrene.

substantial enantioselectivity is destroyed by even small amounts of added sodium citrate. This finding suggests that citrate shunts the dihydroxylation process almost exclusively into a 2nd, non-enantioselective catalytic cycle, like that shown in Figure 6. The two free bystander carboxylate groups in this putative sequence would greatly enhance the hydrophilic environment in the vicinity of the open coordination site under the square pyramid of the Os(VI) complex **v**, and/or the apical oxo group on the opposite side. Such effects operating at these two sites could easily account for the great facility of the glycolate ligand hydrolysis/exchange and, as a consequence, improved rates observed in these systems. We have already seen this "special carboxylate effect" in the studies of dihydroxylation and aminohydroxylation of unsaturated carboxylic acids even under basic conditions, where only the ionized form ($-COO^-$) exists.[17]

In summary, an important new level of mechanistic insight has emerged, with the realization that these are *two* major catalyst-killing scenarios, both pH-dependent: (1) at pH ca. 8 the Os(VI) species **iv** can trap the catalyst, especially for electron-deficient olefins, and (2) at pH ca. 6 Os(VI) disproportionation sets in and the resulting Os(IV) species, being insoluble and inert, are permanently lost from the catalyst pool. However, each of these catalyst inactivation paths is subject to an important caveat: (1) chelating acids, such as citric, effectively prevent Os(VI) disproportionation even under very acidic conditions; and (2) under basic conditions, even the 18-electron dianion **iv** does not block hydrolysis/turnover, when there are $-COO^-$ groups in the resident glycolate ligands.[17]

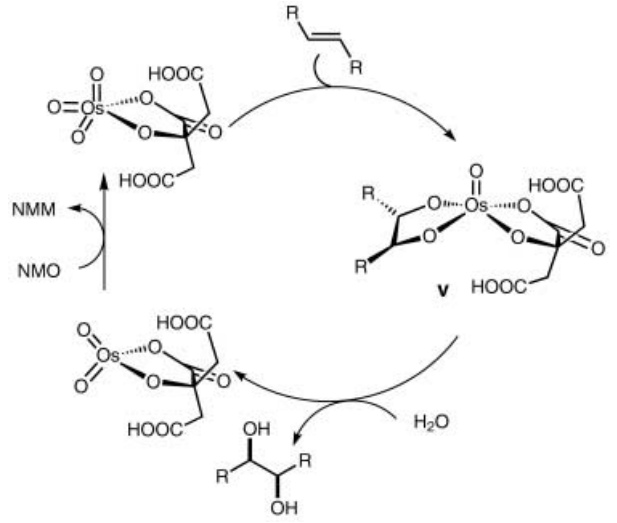


Figure 6. Prevailing catalytic cycle in dihydroxylations with added citric acid.

General Reaction Conditions

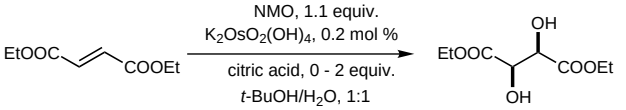
Osmium-catalyzed dihydroxylation of olefins is one of the easiest organic reactions to perform. Water is used as a solvent, and oxygen is not a concern. Systematic studies with many different olefins (*vide infra*) enabled us to put forward two simple procedures, which, together, should encompass most of the "olefin universe". Although the standard conditions call for a 1:1 water/*tert*-butyl alcohol mixture as the solvent, we have successfully used water/acetonitrile as well as water without any organic co-solvent in a number of dihydroxylations. Even if the olefin is not completely soluble, dihydroxylation proceeds in good yields, albeit somewhat slower. The reaction can be performed quite concentrated, 1 M in olefin being standard, which further simplifies product isolation as well as scale-up. Optimization studies have revealed that 0.75 equivalent (in relation to the olefin) of citric acid is sufficient for most substrates, although as much as 2 equivalents may be beneficial for particularly slow dihydroxylations. Usually, reactions are performed with very small amounts of osmium catalyst, only 0.1 to 0.2 mol % required. Osmium tetroxide can be used, but we prefer the stable, non-volatile $K_2OsO_2(OH)_4$. In general, all reactions are performed at ambient temperature, with a few exceptions noted below. In the Experimental Section, typical procedures are given for the case that the diol product precipitates from the reaction mixture (Procedure A) and for the case that the product does not precipitate (Procedure B).

Synthetic Applications

Dihydroxylation of α,β-Unsaturated Esters

These substrates are readily converted to the corresponding diols in excellent yields. Reaction times and product yields depend significantly on the amount of citric acid used. To devise optimal conditions, we studied the dihydroxylation of diethyl fumarate with varied amounts of citric acid. As Table 2 illustrates, best results are obtained when 0.75 equivalent is employed. The optimal substrate concentration is about 1 M. Other

Table 2. Effect of the amount of citric acid on dihydroxylation of diethyl fumarate.



Citric acid [equiv.]	Reaction time [h]	Yield [%]
0	16	33
0.25	16	66
0.5	1.5	90
0.75	0.25	90
2	0.5	90

unsaturated esters show similar trends; therefore, all ester dihydroxylations should be performed in the same way.

As evident from Table 3, the process tolerates a wide variety of functional groups as well as olefins ranging toward the extremely electron-poor end of the spectrum. In most cases, 0.1 mol % of osmium catalyst is sufficient to completely convert olefin into the diol product in 1 to 12 hours, although 0.2 mol % can be used to reduce reaction time to 0.5 – 3 hours. Trisubstituted olefins (Table 4), regardless of the substitution pattern, also participate readily in the reaction. It is noteworthy that in all cases pure, crystalline diols were obtained without any additional purification.

Dihydroxylation of α,β-Unsaturated Amides

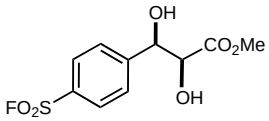
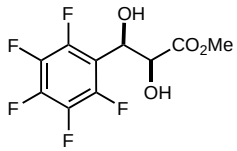
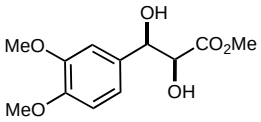
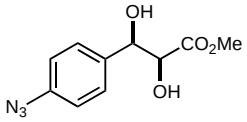
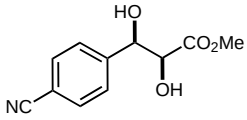
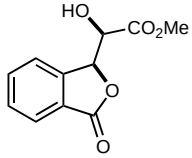
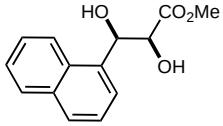
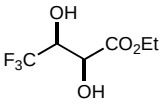
These substrates are generally less reactive than esters, usually requiring 0.2 mol % of osmium catalyst to achieve best results (Table 5). Reaction time varies from 6 to 48 hours. In addition, 2 equivalents of citric acid should be used for secondary amides, which tend to react slower, whereas 0.75 equivalent is sufficient for the tertiary amides.

Dihydroxylation of α,β-Unsaturated Phosphonates

This substrate class is even less reactive than the preceding one, requiring more catalyst than most other olefins (Table 6). Thus, best results were obtained when 0.4 mol % of osmium catalyst was employed.

The amount of citric acid required to achieve high yields is dictated by the nature of the substituents on phosphorus. For more sterically demanding substituents (entries 4 and 5) 2 equivalents should be used. For smaller alkyl esters 0.75 equivalent is usually sufficient.

Table 3. Dihydroxylation of α,β-unsaturated esters.

Entry	Product	Yield [%]	mp [°C]
1		86	151–153
2		99	107–108
3		87	75–78
4		86	82–84
5		84	110–112
6		86	133–135
7		93	124–125
8		83	33

Dihydroxylation of α,β-Unsaturated Nitriles

The successful dihydroxylation of these substrates with this new acidic/chelating ligand-based process is particularly gratifying (Table 7). To the best of our knowledge, it represents the first preparation of α-cyanohydrins by dihydroxylation (catalytic or stoichiometric) of unsaturated nitriles. The products are highly unstable under basic conditions, and the new method allows facile preparation of a range of cyanohydrins in excellent yields.

Table 4. Dihydroxylation of α,β-unsaturated esters.

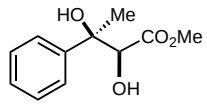
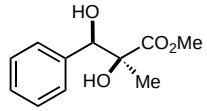
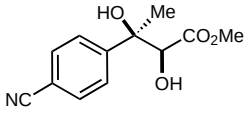
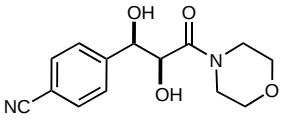
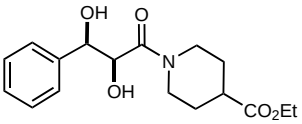
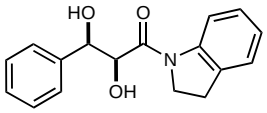
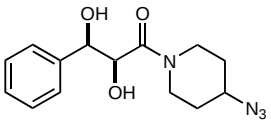
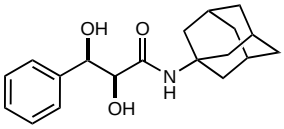
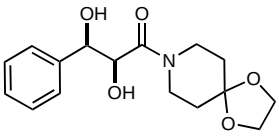
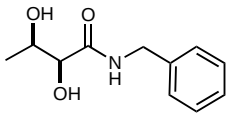
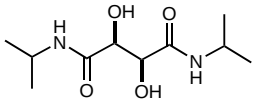
Entry	Product	Yield [%]	mp [°C]
1		95	60–62
2		90	66–67
3		93	103–104

Table 5. Dihydroxylation of α,β-unsaturated amides.

Entry	Product	Yield [%]	mp [°C]
1		99	103
2		97	118–120
3		99	163–164
4		96	82–84
5		98	163–164
6		94	118–119
7		90	123–124
8		85	163–165

Miscellaneous Substrates, Other Oxidants

While difficult to dihydroxylate by other methods,[18] an olefin containing an unprotected tertiary amino group was readily converted to the corresponding diol under acidic conditions (Table 8, entry 1).[19] The extreme water solubility of this diol product led to incorporation of other process changes facilitating product isolation. As a first step, NMO was replaced with trimethylamine *N*-oxide (TMO),[20] to simplify removal of the reduced tertiary amine byproduct. After treating the crude reaction products with a basic ion exchange resin, the mixture was concentrated (trimethylamine evaporated) to give the aminodiol in excellent yield and purity.

Although TMO was previously found to be a less effective oxidant in the standard Upjohn dihydroxylations, it is generally as efficient, and often superior, to NMO under the new, acidic conditions. Trimethylamine is more basic than 4-methylmorpholine (pK_a 9.81 and 7.40, respectively), leading to a greater tendency for the catalyst to be tied up as **iv** (Figure 4) under unbuffered conditions. Thus, diols from both unsaturated amides and phosphonates were readily obtained by this method (Table 8, entries 2 and 3).

Olefins containing tetrazole functionality can be easily prepared from α,β-unsaturated nitriles by a method recently developed in our laboratories.[21] Carrying these heterocyclic olefins forward under the new dihydroxylation conditions furnishes the diols which precipitate from the reaction mixture in virtually quantitative yields (Table 9, entries 1 and 2).

Treatment of the same olefinic tetrazoles with anhydrides of carboxylic acids provides easy access to vinyloxadiazoles, which are also found to be excellent substrates for the dihydroxylation (entries 3 and 4). Even α,β-unsaturated ketones and nitroalkenes, generally regarded as "hopeless" substrates (principally due to the base sensitivity of the products), can be dihydroxylated, providing uniquely functionalized vicinal diols (entries 5 and 6).

Dihydroxylations at Elevated Temperature

The "standard" Upjohn dihydroxylations at elevated temperatures are generally plagued by severely diminished diol yields due to overoxidation of the initial diol product. As a consequence, product isolation and purification is difficult and, except for a few specific substrates, these dihydroxylations are not practical. We are, therefore, glad to report that with added citric acid osmium-catalyzed dihydroxylations can be successfully performed at temperatures exceeding 100 °C without

Table 6. Dihydroxylation of α,β-unsaturated phosphonates.

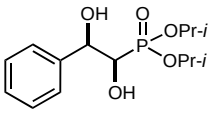
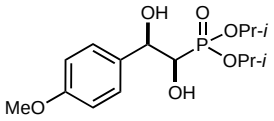
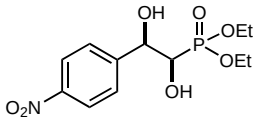
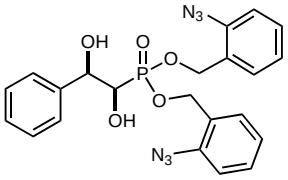
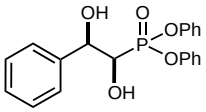
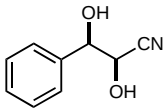
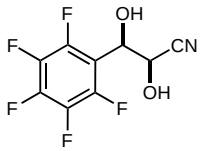
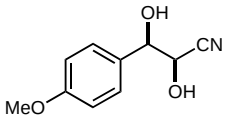
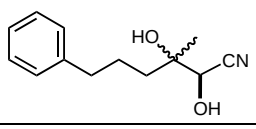
Entry	Product	Yield [%]	mp [°C]
1		98	84–88
2		97	83–85
3		94	88–89
4		87	82–84
5		88	123–125

Table 7. Dihydroxylation of α,β-unsaturated nitriles.

Entry	Product	Yield [%]	mp [°C]
1		99	oil
2		87	108–110
3		93	oil
4		98[a]	oil

[a] Diastereomers arise due to *E*/*Z*-olefin mixture in the α,β-unsaturated nitrile starting material.

Table 8. Dihydroxylations with trimethylamine *N*-oxide (TMO · 2 H_2O).

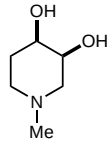
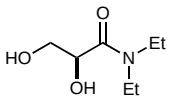
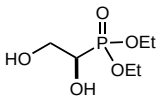
		Yield [%]	
Entry	Product	0.5 equiv. citric acid *t*-BuOH/H_2O 1:1	no additive *t*-BuOH/H_2O 1:1
1		97	<5
2		97	<10
3		91	<5

Table 9. Dihydroxylation of miscellaneous electron-deficient olefins.

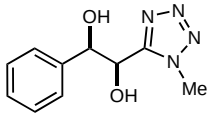
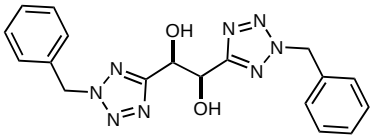
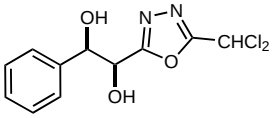
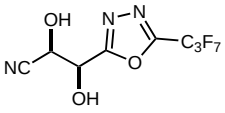
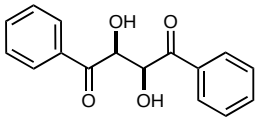
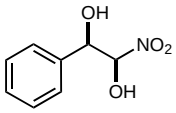
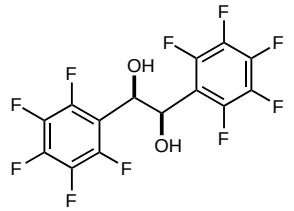
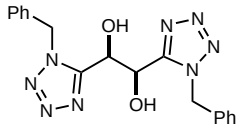
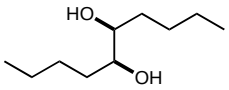
Entry	Product	Yield [%]	mp [°C]
1		90	149 (dec.)
2		95	126–128
3		94	98–101
4		96	99–100
5		90	118–119
6		70	147–149

Table 10. Dihydroxylation at elevated temperatures.

Entry	Product	Temp. [°C]	Yield [%]	mp [°C]
1		120	81	158–160
2		120	97	203 (dec.)
3		60	94[a]	49–52

[a] Under similar conditions, but without added citric acid, the yield of this diol approaches 90%, but the product is obtained as a waxy, dark-brown solid.

any detrimental effect.[22] In fact, pure vicinal diols can be obtained in high yields from olefins that do not participate in dihydroxylation under the otherwise identical conditions, as Table 10 shows.

Conclusion

In conclusion, this modified process for the osmium-(VIII)-catalyzed dihydroxylation of olefins under acidic conditions offers a number of advantages over the original processes run under mildly basic conditions. Above all, it expands the range of the substrates that can now be efficiently dihydroxylated. Citric acid appears to be superior for maintaining the pH in the desired range. Additionally, it affords product diols of exceptional purity. It also allows the reactions to be performed at elevated temperatures without observable catalyst or oxidant loss/decomposition, and without overoxidation of the diol product. Simple product isolation makes this process easy to scale-up. We are presently exploring other oxidants that are amenable to these conditions, and could prove even more convenient and economical than NMO or TMO. In addition, studies on variants of the asymmetric dihydroxylation using chiral, acidic chelating ligands, in place of citric acid are currently underway.[17c]

Experimental Section

Procedure A using 4-Methylmorpholine *N*-Oxide, as Exemplified for Dihydroxylation of *trans*-*N*-cyclohexylcinnamamide; Products Precipitate from the Reaction Mixture

The olefin (22.9 g, 0.1 mol) was suspended in a solution of citric acid (38.4 g, 0.2 mol) in 100 mL of a 1:1 mixture of *tert*-butyl alcohol/water in a 500 mL Erlenmeyer flask. Potassium osmate (0.074 g, 0.2 mol %) was then added, followed by 4-methylmorpholine *N*-oxide [22.8 mL of a 50 % wt. solution in water (Aldrich), 0.11 mol]. *The reaction mixture turned bright green (this color is characteristic for almost all dihydroxylations performed under these acidic conditions)* and was stirred at room temperature for 12 h, after which time it went nearly colorless. The precipitate was then filtered and washed with HCl (1 M, 120 mL), water, and dried to afford the pure diol product, *N*-cyclohexyl-*syn*-2,3-dihydroxy-3-phenylpropionamide, as a white solid. Yield: 26 g (99%); mp 163 – 164 °C.

Procedure B using 4-Methylmorpholine *N*-Oxide, as Exemplified for Dihydroxylation of Ethyl *trans*-4-Bromocrotonate; Products do not Precipitate from the Reaction Mixture

The olefin (19.3 g, 0.1 mol) and citric acid (14.4 g, 0.075 mol) were dissolved in 100 mL of a 1:1 mixture of *tert*-butyl alcohol/water in a 500 mL Erlenmeyer flask. Potassium osmate (0.037 g, 0.1 mol %) was then added followed by 4-methylmorpholine *N*-oxide (22.8 mL of a 50 % wt. solution in water, 0.11 mol). The reaction mixture turned bright green and was stirred at room temperature for 3 h, after which time it went nearly colorless. *tert*-Butyl alcohol was removed on a rotary evaporator, and the aqueous residue was then acidified with HCl (1 M, 120 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried with sodium sulfate and concentrated to give the pure diol product, ethyl (4-bromo-*syn*-2,3-dihydroxy)butyrate, as a colorless oil. Yield: 20.5 g (90%).

Representative Procedure for Preparation of Water-Soluble Diols using Trimethylamine *N*-Oxide as Exemplified for 1-Methyl-1,2,3,6-tetrahydropyridine

To a stirred solution of the hydrochloride salt of the olefin (1.34 g, 10.0 mmol) in *tert*-butyl alcohol/water (1:1, 17 mL) was added trimethylamine *N*-oxide dihydrate (1.11 g, 10.0 mmol), citric acid (0.961 g, 5.00 mmol), and OsO_4 (42.6 mM in CH_3CN, 470 μL, 20.0 μmol). The bright green color faded to a pale yellow as the reaction proceeded (16 h, r.t.). Amberlite IRA-400(OH) anion exchange resin (20 g) was then added. The suspension was stirred for ca. 1 h and then filtered. The resin was washed with water (3 × 10 mL). The filtrate was concentrated on a rotary evaporator at 35 – 40 °C using 3 × 25 mL portions of ethanol to azeotropically remove water. The resulting residue was dried under high vacuum to afford the product, *N*-methyl-3,4-dihydroxypiperidine, as a colorless wax. Yield: 1.27 g (97%); ^{1}H NMR (400 MHz, CD_3OD): δ =

1.74 – 1.81 (m, 1H), 1.90 – 1.96 (m, 1H), 2.47 (s, 3H), 2.58 – 2.64 (m, 1H), 2.71 – 2.75 (m, 3H), 3.79 – 3.80 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 29.8, 45.5, 52.0, 58.1, 68.0, 68.9.

Ethyl (4-Bromo-*syn*-2,3-dihydroxy)butyrate

Obtained as a colorless oil using procedure B. Yield: 90%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.42 (broad s, 1H), 4.31 (q, J = 7.3 Hz, 2H), 4.17 (broad t, J = 6.9 Hz, 1H), 3.51 (dd, J = 6.9 and 2.2 Hz, 2H), 3.24 (broad s, 1H), 2.58 (broad s, 1H), 1.32 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.66, 72.21, 70.71, 62.00, 32.30, 13.80; MS (ES$^+$): m/z = 226.9 (MH^+), 248.9 (M^+Na).

Methyl [*syn*-2,3-Dihydroxy-3-(4-fluorosulfonyl-phenyl)]propionate

Procedure A; white solid; yield: 86%; mp 151 – 153 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.08 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 5.26 (s, 1H), 5.07 (d, J = 6.2 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.31 (d, J = 7.6 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.28, 151.78, 129.87 (d, J = 23 Hz). 128.55, 127.88, 74.65, 73.30, 51.66; ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 99.69; MS (ES$^+$): m/z = 301.0 (M^+Na).

Methyl (*syn*-2,3-Dihydroxy-3-pentafluorophenyl)-propionate

Procedure A; white solid; yield: 99%; mp 107 – 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.35 (d, J = 3.6 Hz, 1H), 4.36 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 173.22, 146.58 (dm, J = 247 Hz), 142.07 (dm, J = 251 Hz), 138.90 (dm, J = 249 Hz), 116.03 (tm, J = 14 Hz), 75.23, 69.17, 52.80; ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 142.82 (dd, J = 23 and 8 Hz), – 153.72 (t, J = 23 and 8 Hz), – 161.35 (td, J = 23 and 8 Hz); MS (ES$^+$): m/z = 309 (M^+Na).

Methyl [*syn*-2,3-Dihydroxy-3-(3,4-dimethoxyphenyl)]-propionate

Procedure B; white solid; yield: 87%; mp 75 – 78 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.07 (d, J = 1.9 Hz, 1H), 6.93 (dd, J = 8.2 and 1.9 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 4.91 (d, J = 3.4 Hz, 1H), 4.50 (broad s, 1H), 4.23 (d, J = 3.4 Hz, 1H), 4.14 (broad s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.11, 148.72, 148.53, 132.50, 118.54, 110.78, 109.55, 75.15, 74.31, 55.78, 55.74, 52.51; MS (ES$^+$): m/z = 279.0 (M^+Na), 535.2 ($2M^+$Na).

Methyl [3-(4-Azidophenyl)-*syn*-2,3-dihydroxy]-propionate

Procedure A; white solid; yield: 86%; mp 82 – 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 4.99 (d, J = 3.0 Hz, 1H), 4.34 (d, J = 3.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.18, 139.80, 136.77, 127.94, 119.07, 74.95, 74.12, 52.96; MS (ES$^+$): m/z = 260.0 (M^+Na).

Methyl [3-(4-Cyanophenyl)-*syn*-2,3-dihydroxy]-propionate

Procedure A; white solid; yield; 84%; mp 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 5.08 (d, J = 2.6 Hz, 1H), 4.36 (d, J = 2.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 174.10, 148.59, 133.04, 128.80, 119.94, 112.09, 76.37, 75.22, 52.77; MS (ES$^+$): m/z = 222.1 (MH^+), 244.1 (M^+Na).

Methyl Hydroxy-(3-oxo-1,3-dihydro-isobenzofuran-1-yl)acetate

Procedure A; white solid; yield: 86%; mp 133 – 135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.7 Hz, 1H), 7.81 (td, J = 7.7 and 1.1 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 5.80 (d, J = 1.8 Hz, 1H), 4.68 (d, J = 1.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.62, 170.01, 147.09, 134.36, 129.50, 126.35, 124.82, 123.15, 81.78, 70.05, 52.29, 52.29; MS (ES$^+$): m/z = 223.1 (MH^+), 245.1 (M^+Na).

Methyl [*syn*-2,3-Dihydroxy-3-(naphth-1-yl)]-propionate

Procedure A; white solid; yield: 93%; mp 124 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.62 – 7.46 (m, 3H), 5.88 (d, J = 2.2 Hz, 1H), 4.57 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.00, 137.37, 133.17, 129.77, 128.86, 127.48, 126.17, 125.39, 125.25, 125.10, 122.60, 74.16, 70.79, 51.66; MS (ES$^+$): m/z = 269.0 (M^+Na), 515.2 ($2M^+$Na).

Ethyl (*syn*-2,3-Dihydroxy-4,4,4-trifluoro)butyrate

Procedure B; white solid; yield: 83%; mp 33 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (s, 1H), 4.38 – 4.28 (m, 3H), 3.60 – 3.40 (m, 1H), 3.27 (broad s, 1H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.67, 124.07 (q, J = 284 Hz), 70.40 (q, J = 31 Hz), 63.56, 14.23; ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 76.71; MS (ES$^+$): m/z = 202.9 (MH^+), 224.9 (M^+Na).

Methyl (*syn*-2,3-Dihydroxy-3-methyl-3-phenyl)-propionate

Procedure B; white solid; yield: 95%; mp 60 – 62 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.55 – 7.48 (m, 2H), 7.35 – 7.26 (m, 2H), 7.25 – 7.18 (m, 1H), 4.36 – 4.21 (m, 3H), 3.61 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.45, 146.05, 127.50, 126.39, 125.77, 78.17, 75.12, 51.14, 25.84; MS (ES$^+$): m/z = 233.1 (M^+Na).

Methyl (*syn*-2,3-Dihydroxy-2-methyl-3-phenyl)-propionate

Procedure A; white solid; yield: 90%; mp 66 – 67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.35 (m, 2H), 7.32 – 7.22 (m, 3H), 5.54 (broad s, 1H), 5.01 (broad s, 1H), 4.69 (s, 1H), 3.67 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.82, 140.65, 128.47, 127.26, 77.44, 77.39, 22.31; MS (ES$^+$): *m/z* = 233.1 (M^+Na).

Methyl [3-(4-Cyanophenyl)-*syn*-2,3-dihydroxy-3-methyl]propionate

Procedure A, white solid; yield: 93%; mp 103 – 104 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.78 – 7.68 (m, 4H), 4.60 (broad s, 1H), 4.50 – 4.35 (m, 2H), 3.64 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.18, 151.90, 131.47, 127.15, 119.29, 109.30, 77.83, 75.25, 51.38, 26.36; MS (ES$^+$): *m/z* = 236.1 (MH^+), 258.0 (M^+Na).

N-Cyclohexyl-*syn*-2,3-dihydroxy-3-phenylpropion-amide

Procedure A; white solid; yield: 99%; mp 163 – 164 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.38 – 7.36 (m, 5H), 7.24 – 7.18 (m, 1H), 5.26 (d, *J* = 6.2 Hz, 1H), 5.23 (d, *J* = 7.3 Hz, 1H), 4.88 – 4.80 (m, 1H), 3.95 – 3.85 (m, 1H), 3.58 – 3.48 (m, 1H), 1.75 – 1.45 (m, 5H), 1.35 – 1.05 (m, 5H); ^{13}C NMR (500 MHz, DMSO-d_6): δ = 170.96, 142.96, 127.55, 126.63, 75.69, 73.50, 47.21, 32.31, 32.29, 25.18, 24.60; MS (ES$^+$): *m/z* = 264.0 (MH^+), 286.0 (M^+Na), 549.3 ($2M^+$Na).

Ethyl 1-(*syn*-2,3-Dihydroxy-3-phenylpropionyl)-piperidine-4-carboxylate

Procedure A; white solid; yield: 97%; mp 118 – 120 °C; slow rotation around the amide bond: 2 rotamers seen by NMR (both ^{1}H and ^{13}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.26 (m, 5H), 4.69 (d, *J* = 5.9 Hz, 0.5 H), 4.65 (d, *J* = 6.2 Hz, 0.5 H), 4.45 (d, *J* = 5.9 Hz, 0.5 H), 4.41 (d, *J* = 6.2 Hz, 0.5 H), 4.39 – 4.32 (m, 0.5H), 4.28 – 4.18 (m, 0.5H), 4.15 – 4.05 (m, 2H), 3.40 – 3.25 (m, 1H), 3.00 – 2.85 (m, 1H), 2.75 – 2.65 (m, 0.5H), 2.45 – 2.30 (m, 1H), 2.25 – 2.10 (m, 0.5H), 1.95 – 1.80 (m, 1H), 1.65 – 1.40 (m, 2.5H), 1.30 – 1.15 (m, 3H), 0.90 – 0.75 (m, 0.5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.86, 173.71, 169.78, 142.12, 141.85, 127.68, 126.89, 74.53, 73.98, 72.43, 59.92, 44.12, 43.91, 40.80, 40.72, 28.33, 27.74, 27.51, 27.38, 14.09; MS (ES$^+$): *m/z* = 322.3 (MH^+), 344.3 (M^+Na).

1-(2,3-Dihydroindol-1-yl)-*syn*-2,3-dihydroxy-3-phenyl-propan-1-one

Procedure A; white solid; yield: 99%; mp 163 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.2 Hz, 1H), 8.45 – 8.38 (m, 2H), 8.35 – 8.27 (m, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 4.84 (d, *J* = 6.4 Hz, 1H), 4.32 (d, *J* = 6.4 Hz, 1H), 3.87 – 3.74 (m, 1H), 3.33 (broad s, 2H), 3.05 – 2.88 (m, 2H), 2.80 – 2.65 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.18, 142.68, 141.94, 131.91, 127.73, 127.12, 126.92, 126.89, 124.80, 123.68, 116.50, 74.81, 73.69, 47.26, 27.60; MS (ES$^+$): *m/z* = 284.1 (MH^+), 306.1 (M^+Na).

1-(4-Azido-piperidin-1-yl)-*syn*-2,3-dihydroxy-3-phenyl-propan-1-one

Procedure A; white solid; yield: 96%; mp 111 °C; slow rotation around the amide bond: 2 rotamers seen by NMR (both ^{1}H and ^{13}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.26 (m, 5H), 4.67 (t, *J* = 6.4 Hz, 1 H), 4.45 – 4.35 (m, 1H), 4.05 – 3.95 (m, 0.5H), 3.90 – – 3.80 (m, 0.5H), 3.60 – 3.45 (m, 1H), 3.40 – 3.25 (m, 1H), 3.25 – 3.15 (m, 0.5 H), 3.10 – 3.00 (m, 0.5H), 3.00 – 2.90 (m, 0.5H), 2.55 – 2.45 (m, 0.5H), 1.90 – 1.70 (m, 1H), 1.65 – 1.25 (m, 2.5H), 0.85 – 0.75 (m, 0.5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.90, 142.03, 141.82, 127.73, 127.65, 127.12, 126.97, 74.59, 74.13, 72.54, 72.45, 56.75, 42.72, 42.44, 30.73, 30.36, 30.00; MS (ES$^+$): *m/z* = 291.1 (MH^+), 313.1 (M^+Na).

N-(Adamant-1-yl)-*syn*-2,3-dihydroxy-3-phenyl-propionamide

Procedure A; white solid; yield: 98%; mp 163 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.28 (m, 5H), 5.84 (s, 1H), 4.99 (d, *J* = 4.7 Hz, 1H), 4.10 (s, 1H), 3.44 (broad s, 1H), 3.19 (broad s, 1H), 2.04 (s, 3H), 1.89 (s, 6H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.11, 143.09, 127.59, 126.68, 75.69, 73.42, 50.55, 41.04, 36.04, 28.88; MS (ES$^+$): *m/z* = 316.3 (MH^+), 653.7 ($2M^+$Na).

1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-*syn*-2,3-dihydroxy-3-phenylpropan-1-one

Procedure A, white solid; yield: 94%; mp 118 – 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.28 (m, 5H), 4.69 (d, *J* = 5.9 Hz, 1H), 4.46 (d, *J* = 5.9 Hz, 1H), 3.98 – 3.86 (m, 4H), 3.82 – 3.70 (m, 1H), 3.60 – 3.50 (m, 1H), 3.25 – 3.15 (m, 1H), 2.92 – 2.82 (m, 1H), 1.68 – 1.52 (m, 2H), 1.50 – 1.40 (m, 1H), 1.14 – 1.04 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.85, 141.91, 127.71, 127.09, 126.91, 106.25, 74.42, 72.52, 63.82, 42.86, 34.84, 34.23; MS (ES$^+$): *m/z* = 308.3 (MH^+), 330.2 (M^+Na), 637.5 ($2M^+$Na).

N-Benzyl-*syn*-2,3-dihydroxybutyramide

Procedure A; white solid; yield: 90%; mp 123 – 124 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 8.24 (s, 1H), 7.40 – 7.25 (m, 4H), 7.25 –7.15 (m, 1H), 4.47 – 4.42 (m, 2H), 4.08 (qd, *J* = 6.2 and 3.0 Hz, 1H), 3.89 (d, *J* = 3.0 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.86, 139.68, 128.26, 127.26, 126.73, 75.39, 67.67, 41.87, 19.73; MS (ES$^+$): *m/z* = 210.1 (MH^+), 232.1 (M^+Na).

Syn-2,3-Dihydroxy-*N,N'*-di*iso*propylsuccinamide

Procedure A; white solid; yield: 85%; mp 163 – 165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33 (d, *J* = 8.2 Hz, 2H), 5.49 (broad s, 2H), 4.16 (s, 2H), 3.96 – 3.82 (m, 2H), 1.06 (d,

$J = 6.5$ Hz, 12H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 171.04$, 72.54, 40.31, 22.48; MS (ES$^+$): $m/z = 233.3$ (MH$^+$).

Di*iso*propyl (*syn*-1,2-Dihydroxy-2-phenylethyl)-phosphonate

Procedure B; white solid; yield: 98%; mp 84 – 88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.50 - 7.26$ (m, 5H), 5.14 – 5.06 (m, 1H), 4.90 – 4.65 (m, 2H), 3.95 (dd, $J = 8.4$ and 2.6 Hz, 1H), 3.55 (broad s, 1H), 1.36 (d, $J = 6.2$ Hz, 6H), 1.28 (t, $J = 6.2$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 142.48$ (d, $J = 9$ Hz), 127.64, 127.20, 126.98, 72.60 (d, $J = 6$ Hz), 72.20 (d, $J = 163$ Hz), 70.19 (d, $J = 8$ Hz), 69.42 (d, $J = 8$ Hz), 24.14 (d, $J = 3$ Hz), 23.85 (d, $J = 5$ Hz), 23.59 (d, $J = 5$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 21.6$; MS (ES$^+$): $m/z = 303.0$ (MH$^+$), 627.2 (2M$^+$Na).

Di*iso*propyl [*syn*-1,2-Dihydroxy-2-(4-methoxyphenyl)-ethyl]phosphonate

Procedure A; white solid; yield: 97%; mp 83 – 85 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.34$ (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.04 (t, $J = 4.0$ Hz, 1H), 4.90 – 4.65 (m, 2H), 3.91 (dd, $J = 8.0$ and 3.0 Hz, 1H), 3.79 (s, 3H), 3.55 (broad s, 1H), 1.35 (d, $J = 6.2$ Hz, 6H), 1.27 (t, $J = 6.0$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 158.53$, 134.45 (d, $J = 8$ Hz), 128.33, 113.06, 72.32 (d, $J = 164$ Hz), 72.21 (d, $J = 6$ Hz), 70.17 (d, $J = 8$ Hz), 69.37 (d, $J = 8$ Hz), 24.16, 23.85 (d, $J = 5$ Hz), 23.57 (d, $J = 5$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 21.7$; MS (ES$^+$): $m/z = 687.3$ (2M$^+$Na).

Diethyl [*syn*-1,2-Dihydroxy-2-(4-nitrophenyl)-ethyl]-phosphonate

Procedure A; white solid: yield: 94%; mp 88 – 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 8.5$ Hz, 2H), 5.23 – 5.19 (m, 1H), 4.30 – 4.15 (m, 4H), 4.04 (dd, $J = 9.3$ and 2.0 Hz, 1H), 1.38 (t, $J = 7.0$ Hz, 6H), 1.32 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 150.6$ (d, $J = 10$ Hz), 146.61, 128.36, 122.77, 72.03 (d, $J = 5$ Hz), 71.55 (d, $J = 160$ Hz), 62.08 (d, $J = 6$ Hz), 61.07 (d, $J = 8$ Hz), 16.37 (d, $J = 5$ Hz), 16.19 (d, $J = 5$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 22.6$; MS (ES$^+$): $m/z = 320.0$ (MH$^+$), 342.0 (M$^+$Na).

Bis(2-azidobenzyl) (*syn*-1,2-Dihydroxy-2-phenyl-ethyl)phosphonate

Procedure A; white solid; yield: 87%; mp 107 °C; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.46 - 7.35$ (m, 5H), 7.34 – 7.28 (m, 2H), 7.27 – 7.07 (m, 6H), 5.11 (dd, $J = 12.4$ and 7.3 Hz, 1H), 5.05 (dd, $J = 12.4$ and 7.9 Hz, 1H), 5.00 (t, $J = 5.0$ Hz, 1H), 4.92 (dd, $J = 12.3$ and 7.6 Hz, 1H), 4.76 (dd, $J = 12.3$ and 8.6 Hz, 1H), 4.15 (dd, $J = 9.0$ and 5.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 142.28$ (d, $J = 11$ Hz), 137.04 (d, $J = 5$ Hz), 129.71, 129.62, 129.35 (d, $J = 5$ Hz), 127.91 (d, $J = 6$ Hz), 127.70, 127.52 (d, $J = 6$ Hz), 127.07, 127.04, 124.94, 124.89, 118.46, 72.38 (d, $J = 5$ Hz), 72.29 (d, $J = 157$ Hz), 62.45 (d, $J = 6$ Hz), 61.98 (d, $J = 6$ Hz); ^{31}P NMR (162 MHz, CD_3OD): $\delta = 25.37$; MS (ES$^+$): $m/z = 983.5$ (2M$^+$Na).

Diphenyl (*syn*-1,2-Dihydroxy-2-phenylethyl)-phosphonate

Procedure A; white solid; yield: 88%; mp 125 – 123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45 - 7.05$ (m, 15H), 5.31 (dd, $J = 5.0$ and 3.0 Hz, 1H), 4.35 (dd, $J = 6.5$ and 3.0 Hz, 1H), 3.62 (broad s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 150.52$ (d, $J = 9$ Hz), 149.96 (d, $J = 9$ Hz), 142.05 (d, $J = 10$ Hz), 129.76, 129.58, 127.82, 127.24, 125.04, 124.83, 120.85 (d, $J = 5$ Hz), 120.72 (d, $J = 3$ Hz), 72.39 (d, $J = 6$ Hz), 72.15 (d, $J = 160$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 15.96$; MS (ES$^+$): $m/z = 763.3$ (2M$^+$Na).

syn-2,3-Dihydroxy-3-phenylpropionitrile

Procedure B; colorless oil; yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (s, 5H), 4.73 (d, $J = 6.7$ Hz, 1H), 4.50 (broad s, 2H), 4.39 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.12, 129.18, 128.78, 127.01, 118.29, 74.69, 66.15$; MS (ES$^+$): $m/z = 186.1$ (M$^+$Na).

syn-2,3-Dihydroxy-3-pentafluorophenylpropionitrile

Procedure A; white solid; yield: 87%; mp 108 – 110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.01$ (d, $J = 7.0$ Hz, 1H), 6.73 (d, $J = 5.3$ Hz, 1H), 5.14 – 5.02 (m, 1H), 4.80 (t, $J = 7.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.85$ (dm, $J = 250$ Hz), 140.49 (dm, $J = 250$ Hz), 137.08 (dm, $J = 250$ Hz), 118.93, 113.49 (t, $J = 15$ Hz), 67.17, 63.87; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -139.48$ (dd, $J = 23$ and 8 Hz), -153.35 (t, $J = 23$ Hz), -161.76 (td, $J = 23$ and 8 Hz); MS (ES$^+$): $m/z = 275.9$ (M$^+$Na).

syn-2,3-Dihydroxy-3-(4-methoxyphenyl)-propionitrile

Procedure B; pale yellow oil; yield: 93%; ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 7.$ 42 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 5.55 (d, $J = 5.9$ Hz, 1H), 5.02 (d, $J = 4.0$ Hz, 1H), 4.85 – 4.75 (m, 1H), 4.70 – 4.58 (m, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 160.69$, 132.37, 129.38, 119.81, 114.27, 75.01, 67.45, 55.55; MS (ES$^+$): $m/z = 216.1$ (M$^+$Na).

1-(1-Methyl-1*H*-tetrazol-5-yl)-2-phenylethane-*syn*-1,2-diol

Procedure A; white solid; yield: 90%; decomposition: 149 °C; ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 7.40 - 7.20$ (m, 5H), 5.30 – 5.22 (m, 1H), 5.20 – 5.14 (m, 1H), 5.13 – 5.06 (m, 1H), 4.98 – 4.90 (m, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 154.99$, 141.04, 127.85, 127.48, 126.91, 75.15, 69.34, 34.31; MS (ES$^+$): $m/z = 221.1$ (MH$^+$), 243.1 (M$^+$Na), 463.1 (2M$^+$Na).

1-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(2-benzyl-2*H*-tetrazol-5-yl)-ethane-*syn*-1,2-diol

Procedure B; waxy solid; yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.25 (m, 10H), 5.74 – 7.67 (m, 4H), 5.63 (d, *J* = 3.4 Hz, 1H), 5.37 (d, *J* = 3.4 Hz, 1H), 4.47 (broad s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.01, 153.60, 133.68, 132.87, 129.10, 129.02, 128.75, 128.53, 128.34, 67.86, 67.16, 57.00, 51.78; MS (ES$^+$): *m/z* = 379.0 (MH$^+$).

1-(5-Dichloromethyl-[1,3,4]oxadiazol-2-yl)-2-phenyl-ethane-*syn*-1,2-diol

Procedure A; white solid; yield: 94%; mp 98 – 101 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.91 (s, 1H), 7.35 – 7.15 (m, 5H), 6.45 (broad s, 1H), 5.92 (broad s, 1H), 4.94 (d, *J* = 6.5 Hz, 1H), 4.86 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.02, 162.26, 140.65, 127.97, 127.59, 126.72, 74.95, 70.31, 58.66; MS (ES$^+$): *m/z* = 289.0 (MH$^+$), 311.0 (M$^+$Na).

syn-2,3-Dihydroxy-3-(5-heptafluoropropyl-[1,3,4]oxadiazol-2-yl)-propionitrile

Procedure A; white solid; yield: 96%; mp 99 – 101 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.24 (d, *J* = 5.9 Hz, 1H), 7.07 (d, *J* = 6.5 Hz, 1H), 5.27 (t, *J* = 5.3 Hz, 1H), 5.01 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.16, 154.63 (t, *J* = 30 Hz), 121.43, 117.87 (qt, *J* = 288 and 34 Hz), 108.80 (tt, *J* = 259 and 32 Hz), 107.80 (tm, *J* = 267 Hz), 66.50, 63.15; ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 79.14 (t, *J* = 7.6 Hz), – 112.92 (m), – 125.88 (s); MS (ES$^+$): *m/z* = 324.0 (MH$^+$), 346.0 (M$^+$Na).

2,3-*syn*-Dihydroxy-1,4-diphenylbutane-1,4-dione

Procedure B; white slid; yield: 90%; mp 118 – 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 – 7.97 (m, 4H), 7.74 – 7.68 (m, 2H), 7.65 – 7.58 (m, 4H), 5.38 (s, 2H), 3.93 (broad s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.80, 134.33, 133.89, 129.31, 128.38, 74.79; MS (ES$^+$): *m/z* = 271.0 (MH$^+$), 293.0 (M$^+$Na).

1-Nitro-2-phenylethane-*syn*-1,2-diol

Procedure B; white solid; yield: 70%; mp 147 – 149 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43 (d, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 1H), 6.34 (d, *J* = 5.1 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 2H), 5.32 (s, 1H), 5.22 – 5.14 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.72, 127.70, 126.97, 126.90, 91.63, 69.55; MS (ES$^+$): *m/z* = 271.0 (MH$^+$), 293.0 (M$^+$Na).

1,2-Bis(pentafluorophenyl)ethane-*syn*-1,2-diol

Procedure A; white solid; yield: 81%; mp 158 – 160 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 5.47 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 146.50 (dm, *J* = 247 Hz), 142.36 (dm, *J* = 254 Hz), 138.91 (dm, *J* = 252 Hz), 115.63 (t, *J* = 15 Hz), 69.02; ^{19}F NMR (376 MHz, CD_3OD): δ = – 142.72 (d, *J* = 15 Hz), – 155.86 (t, *J* = 23 Hz), – 163.69 (td, *J* = 23 and 8 Hz); MS (ES$^+$): *m/z* = 417.0 (M$^+$Na).

1,2-Bis(1-benzyl-1*H*-tetrazol-5-yl)ethane-*syn*-1,2-diol

Procedure A; white solid; yield: 97%; decomposition: 203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.37 (s, 10H), 6.92 (d, *J* = 5.0 Hz, 2H), 5.84 (d, *J* = 15.3 Hz, 2H), 5.77 (d, *J* = 15.3 Hz, 2H), 5.51 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.37, 134.92, 128.74, 128.33, 66.37, 50.85; MS (ES$^+$): *m/z* = 379.1 (MH$^+$).

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[8] The following automation equipment was used in these studies. Solutions of the additives for screening were prepared using Bohdan weighing-dissolution station, capable of preparing 192 solutions with a defined concentration in each run. Gilson 215 liquid handler was used to prepare reaction mixtures and to take aliquots for analysis at predefined time intervals. The yield of the diol **2** was quantitatively analyzed by mass spectrometry. For additional details, see A. A. Thomas, *Ph. D. dissertation*, The Scripps Research Institute, **2000**; *Diss. Abstr. Int. B* **2000**, *61(3)*, 1421; J. P. Chiang, *Ph. D. dissertation*, The Scripps Research Institute, **2000**; *Diss. Abstr. Int. B* **2000**, *61(3)*, 1410.

[9] Direct diol quantification using electrospray ionization mass spectrometry (ESI-MS) greatly increases analytical throughput, as each run takes as little as 90 seconds. With proper calibration, the accuracy of this method is as good as quantitative LC analysis. See also: A. E. Rubin, *Ph. D. Dissertation*, The Scripps Research Institute, **1999**; *Diss. Abstr. Int. B* **1999**, *60(6)*, 2705.

[10] The substrates shown in Table 1 were additionally dihydroxylated under the "Sharpless–Akashi" conditions with TBHP as the stoichiometric oxidant and Et_4NOAc as turnover-facilitating additive. With the exception of fumarate, the yields were significantly lower compared to the new acidic conditions. Overoxidation byproducts were also always observed.

[11] Many other catalytic osmylation procedures often give products tinged from gray to brown or black due to traces of osmium complexes entrained as impurities.

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